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Utilization and costs of prescription medication in patients with type 1 diabetes:

Impact of diabetic kidney disease

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ACADEMIC DISSERTATION

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To Kari, Sara and Tomi

“It always seems impossible until it’s done.” *N. Mandela*

“Disease is the biggest money maker in our economy.” *John H. Tobe*

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

- I Lithovius R, Harjutsalo V, Forsblom C, Groop PH, on behalf of the FinnDiane Study. Cumulative cost of prescription medication in outpatients with type 1 diabetes in Finland. *Diabetologia* 54:496-503, 2011
- II Lithovius R, Harjutsalo V, Saraheimo M, Forsblom C, Groop PH, on behalf of the FinnDiane Study. Longitudinal trends in use and costs of prescription medication in patients with type 1 diabetes: The impact of renal disease. *AnnMed* 45:112-119, 2013
- III Lithovius R, Harjutsalo V, Forsblom C, Saraheimo M, Koskinen P, Groop PH, on behalf of the FinnDiane Study. Trends in use and costs of prescription medication in patients with type 1 diabetes: 9-year follow-up after kidney transplantation. *JDM* 3:1-10, 2013
- IV Lithovius R, Harjutsalo V, Forsblom C, Saraheimo M, Groop PH, on behalf of the FinnDiane Study. Antihypertensive treatment and resistant hypertension in patients with type 1 diabetes by stages of diabetic nephropathy. *Diabetes Care* 37:709-717, 2014
- V Lithovius R, Harjutsalo V, Forsblom C, Saraheimo M, Groop PH, on behalf of the FinnDiane Study. The consequences of failure to achieve targets of guidelines for prevention and treatment of diabetic complications in patients with type 1 diabetes. *Acta Diabetol* 52:31-38, 2015

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ABBREVIATIONS

ACE	angiotensin-converting enzyme
ACR	albumin-to-creatinine ratio
ADA	American Diabetes Association
AER	albumin excretion rate in urine
AGE	advanced glycation end-products
Apo	apolipoprotein
ARB	angiotensin receptor blocker
ATC	Anatomical Therapeutic Chemical
BMD	bone and mineral metabolism disorders
BMI	body mass index
BP	blood pressure
CAN	cardiovascular autonomic neuropathy
CD	coeliac disease
CHD	coronary heart disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COI	cost-of-illness
COPD	chronic obstructive pulmonary disease
CPI	Consumer Price Index
CSII	continuous subcutaneous insulin infusion
CVD	cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DDD	Defined Daily Dose
DN	diabetic nephropathy
DPN	diabetic peripheral neuropathy
DPR	Drug Prescription Register
DR	diabetic retinopathy
DRR	Drug Reimbursement Register
EDIC	Epidemiology of Diabetes Interventions and Complications
eGDR	estimated glucose disposal rate
eGFR	estimated glomerular filtration rate
EPO	erythropoietin
ESA	erythrocyte stimulating agents
ESRD	end-stage renal disease
FIMEA	Finnish Medicines Agency
FinnDiane	Finnish Diabetic Nephropathy Study
GLMM	generalized linear mixed models
HbA _{1C}	glycosylated haemoglobin
HDL-C	high-density lipoprotein cholesterol
HILMO	Finnish Care Register for Health Care
HR	hazard ratio
ICD	International Classification of Diseases
LDL-C	low-density lipoprotein cholesterol

MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
MMF	mycophenolate mofetil
MODY	maturity-onset diabetes of the young
MS	multiple sclerosis
MVD	macrovascular disease
NHI	Finnish National Health Insurance
PAD	peripheral arterial disease
PPB	Pharmaceuticals Pricing Board (HILA)
RA	rheumatoid arthritis
RAAS	renin-angiotensin-aldosterone system
RH	resistant hypertension
SD	standard deviation
TSH	thyroid-stimulating hormone
UKPDS	United Kingdom Prospective Diabetes Study
VAT	Value Added Tax
VLDL	very-low-density lipoprotein
WHO	World Health Organization
WHR	waist-to-hip ratio
WPI	Wholesale Price Index

ABSTRACT

Background

The annual incidence rate of type 1 diabetes is increasing on average by 2.5–3% worldwide. Notably, among Finnish children aged below 15 years the rate is continuously the world's highest. About one-third of the patients develop diabetic nephropathy (DN), which is the most severe and burdensome complication, ultimately leading to end-stage renal disease (ESRD), requiring dialysis or kidney transplantation. DN is frequently related to other microvascular complications and cardiovascular diseases. In addition, type 1 diabetes is associated with other chronic conditions such as autoimmune diseases and psychiatric disorders. Therefore, pharmaceutical interventions play an important role not only in controlling glycaemia, but also in treating related co-morbidities. Prescription medications cover about one-third of the total costs of type 1 diabetes. However, patients with type 1 diabetes at different disease severity stages are likely to require different types and amounts of medication as well as other treatments, consequently having different resource needs. Hence, it is important to identify the potential subgroups of patients with greater needs as well as the major cost drivers in order to improve understanding of the cost structure of diabetes care. There is strong evidence that guidelines-based care can improve patient outcomes. Thus, it is also crucial to analyse to what extent the targets of the guidelines are achieved in normal clinical settings, and furthermore, how achievement of the most relevant targets affects the prognosis of patients.

Aims

The use and costs of prescription medication in patients with type 1 diabetes, stratified by various severity stages of the diabetic kidney disease, were evaluated. The implementation of the American Diabetes Association (ADA) guidelines was also studied by evaluating the achievement of treatment targets and how these achievements predict the prognosis of patients at different severity stages of the disease.

Subjects and methods

All participants included in the study were part of the ongoing, nationwide, multicentre Finnish Diabetic Nephropathy Study (FinnDiane), with the main aim of identifying genetic, clinical and environmental risks factors for diabetic complications among patients with type 1 diabetes. The study was launched in 1997 and approximately 4800 individuals have been recruited from 92 centres all over Finland. To obtain information on all purchases of prescription medications as well as co-morbidities and premature mortality, the FinnDiane data were linked with several national registers. Substudies I–III and V have a longitudinal and prospective design, while Study IV was cross-sectional, using baseline data only.

Results

Although diabetes itself generates high medication costs, the progression to more severe stages of DN increases the costs considerably, even before the development of ESRD. In patients with ESRD, the 11-year cumulative costs increased fourfold

(12 470 € vs. 65 480 €), or even 15-fold (3830 € vs. 60 140 €), when diabetes medications were excluded compared with those without severe complications. The cost of diabetes medications remained quite stable irrespective of the presence of complications and duration of diabetes. The major cost drivers were immunosuppressants, peritoneal dialytics and erythropoietin. In general, the increasing trend in the total costs of prescription medications reflects the general development of drug costs in Finland. After generic substitution was introduced in 2003, the cost of lipid-lowering drugs and agents acting on the renin-angiotensin-aldosterone system dropped, although the number of users increased at the same time in all renal status groups prior to ESRD. The costs were significantly higher in patients with macroalbuminuria than in those with earlier stages of DN, and the gap continued to increase until the end of follow-up. A large gap exists between evidence-based diabetes guidelines and clinical practice since only a minority of all patients with type 1 diabetes reached the targets for glycosylated haemoglobin (HbA_{1C}), blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) proposed by the ADA. One of the novel findings was the high prevalence of treatment-resistant hypertension (RH) in patients with type 1 diabetes. RH increased in parallel with the worsening of DN; while less than one-tenth of antihypertensive drug-treated normo- or microalbuminuric patients met the criteria for RH, up to one-third of patients with macroalbuminuria and 40% of patients on dialysis were classified as having RH. Notably, glycaemic, BP and lipid control were also suboptimal among those with no signs or with early signs of diabetic complications. According to our data, failure to reach the ADA targets was associated with increased risk of cardiovascular disease (CVD) and all-cause mortality in patients with type 1 diabetes.

Conclusions

Progression to a more severe stage of DN has a substantial impact on prescription medication costs, highlighting the importance of early intervention to prevent or delay the onset of diabetic kidney disease in patients with type 1 diabetes. In addition, this study revealed that the treatment targets of HbA_{1C}, BP and LDL-C proposed by the ADA have not been achieved. Achievement of these targets would be desirable for the optimal prevention of CVD and mortality in patients with type 1 diabetes.

TIIVISTELMÄ

Taustaa

Tyypin 1 diabeteksen ilmaantuvuus lisääntyy maailmanlaajuisesti keskimäärin 2.5–3% vuodessa. Kansainvälisesti katsoen Suomella on kuitenkin erityisasema tyypin 1 diabeteksen suhteen: suomalaisen lapsen riski sairastua diabetekseen on edelleen maailman korkein. Noin kolmasosa tyypin 1 diabeetikoista sairastuu munuaissairauteen, niin kutsuttuun diabeettiseen nefropatiaan. Se on yksi vakavimmista ja hankalimmista komplikaatioista, erityisesti johtaessaan loppuvaiheen munuaissairauteen (ESRD), joka vaatii dialyysihoitoa tai munuaisen siirron. Nefropatiaan liittyy usein myös muita mikrovaskulaarisia komplikaatioita sekä sydän- ja verisuonitauteja. Lisäksi tyypin 1 diabeetikolla voi olla muita kroonisia sairauksia, kuten autoimmuunisairauksia tai psyykkisiä häiriöitä. Siksi lääkehoidolla on keskeinen merkitys paitsi diabeteksen, myös lisäsairauksien hoidossa. Tyypin 1 diabeteksen kokonaiskustannuksista noin kolmannes aiheutuu reseptilääkkeistä. On kuitenkin todennäköistä, että munuaissairauden vaikeusaste vaikuttaa käytettyihin lääkkeisiin ja niiden määrään, kuten myös muihin tarvittaviin hoitoihin ja taloudellisiin resursseihin. Diabeteksen hoidon kustannusrakenteen ymmärtämiseksi on tärkeää tarkastella lääkkeiden käyttöä eri potilasryhmissä sairauden vaikeusasteiden mukaan sekä määritellä suurimmat kustannusten aiheuttajat. On vahvaa näyttöä siitä, että diabeteksen hoitosuosituksen tavoitteiden toteutuminen vaikuttaa suotuisasti hoitotuloksiin. Siksi on tärkeää myös arvioida, kuinka nämä hoitosuositukset toteutuvat käytännössä ja kuinka kaikkein tärkeimpien hoitotavoitteiden saavuttaminen vaikuttaa potilaan ennusteeseen.

Tavoitteet

Väitöskirjassa tavoitteena oli tarkastella tyypin 1 diabeetikoiden reseptilääkkeiden käyttöä ja kustannuksia munuaissairauden eri vaikeusasteiden mukaan. Toisena tavoitteena oli arvioida American Diabetes Associationin (ADA) hoitosuosituksen toteutumista sekä sitä, miten tavoitteiden toteutuminen vaikuttaa potilaan ennusteeseen munuaissairauden eri vaiheissa.

Tutkimusaineisto ja menetelmät

Tutkimuksen aineisto muodostui FinnDiane-tutkimukseen (Finnish Diabetic Nephropathy Study) osallistuneista tyypin 1 diabeetikoista. FinnDiane on vuonna 1997 aloitettu, yhä jatkuva kansallinen monikeskustutkimus (mukana noin 4800 potilasta 92 keskuksista kaikkialta Suomesta), jonka keskeisenä tavoitteena on tunnistaa perintö- ja ympäristötekijöiden joukosta diabeteksen lisäsairauksille altistavia riskitekijöitä. Tiedot potilaiden reseptilääkeostoista, lisäsairauksista ja kuolleisuudesta saatiin yhdistämällä FinnDiane-aineisto kansallisiin rekistereihin. Osatutkimukset I–III sekä V ovat prospektiivisiä pitkittäistutkimuksia, kun taas osatutkimus IV on poikittaistutkimus, jossa tiedot kerättiin ensimmäiseltä tutkimuskäynniltä.

Tulokset

Vaikka diabetes itsessään aiheuttaa merkittäviä lääkekustannuksia, munuaissairauden eteneminen lisää kustannuksia huomattavasti, jopa ennen loppuvaiheen munuaissairauden

kehittymistä. Munuaissairauden loppuvaiheessa potilaiden 11 vuoden kumulatiiviset lääkekustannukset olivat nelinkertaiset verrattuna niihin, joilla ei ollut vakavia komplikaatioita. Kun diabeteslääkkeet suljettiin pois tarkastelusta, nousivat kustannukset 15-kertaisiksi. Sitä vastoin diabeteslääkkeiden kustannukset eivät juuri vaihdelleet diabeteksen keston ja vakavien komplikaatioiden esiintymisen mukaan. Suurimmat kustannukset aiheutuivat hyljinnänestolääkkeistä, peritoneaalidialyysinesteistä ja erytropoietiinista. Yleisesti ottaen tyypin 1 diabeetikoiden reseptilääkkeiden kokonaiskustannukset kasvoivat seurantajakson aikana, mikä heijastelee yleistä lääkekustannusten kehitystä Suomessa. Vuonna 2003 voimaan tullut lääkevaihto eli geneerinen substituo alensi erityisesti lipidejä muuntavien ja reniini-angiotensiinijärjestelmään vaikuttavien lääkkeiden kustannuksia, vaikka kyseisten lääkkeiden käyttäjien määrät lisääntyivät samanaikaisesti sekä normo-, mikro- että makroalbumiiniuria ryhmissä. Reseptilääkekustannukset olivat merkittävästi korkeammat makroalbumiiniuria ryhmässä kuin normo- ja mikroalbumiiniuriaryhmissä, ja erot suurenivat seurantajakson aikana. Tutkimuksemme osoitti, että näyttöön perustuvien diabeteksen hoitosuosittelujen ja käytännön välillä on suuri ero, sillä vain pieni osa tyypin 1 diabeetikoista saavutti ADA:n suosittelemat HbA_{1C}:n, verenpaineen ja LDL-kolesterolin hoitotavoitteet. Yksi tutkimuksemme keskeisistä ja uusista tuloksista osoitti, että hoidolle resistentti verenpaine on varsin yleistä tyypin 1 diabeetikoilla. Hoidolle resistentti verenpaine lisääntyy kuitenkin munuaissairauden edetessä: verenpainelääkkeitä käyttävistä normo- ja mikroalbumiiniuriapotilaista noin joka kymmenennellä, makroalbumiiniuria- ja munuaisensiirtopotilaista kolmasosalla sekä dialyysipotilaista 40 %:lla esiintyi resistenttiä verenpainetta. On kuitenkin tärkeää huomata, että myös ne, joilla ei ollut lainkaan tai joilla oli vasta alkavia merkkejä munuaissairaudesta, eivät saavuttaneet HbA_{1C}:lle, verenpainelle ja LDL-kolesterolille asetettuja tavoitteita. Tutkimustulostemme mukaan niillä, jotka eivät saavuttaneet hoitotavoitteita, oli suurempi sydän- ja verisuonitautien ja kuoleman riski.

Johtopäätökset

Munuaissairauden etenemisellä on huomattava vaikutus reseptilääkekustannuksiin, jopa ennen munuaissairauden loppuvaiheen kehittymistä. Tutkimustulostemme valossa munuaissairauden ennaltaehkäisyllä, varhaisella toteamisella ja hoidolla on tärkeä merkitys tyypin 1 diabeetikoiden lääkekustannusten hillitsemisessä. Tulokset kuitenkin osoittavat, että ADA:n suosittelemia HbA_{1C}:n verenpaineen ja LDL-kolesterolin hoitotavoitteita ei ole saavutettu, vaikka niiden menestyksellinen täytäntöön paneminen olisi tärkeää sydän- ja verisuonisairauksien ennaltaehkäisemiseksi ja tyypin 1 diabetespotilaiden kuolleisuuden vähentämiseksi.

1 INTRODUCTION

Diabetes is one of the most costly and burdensome chronic diseases of our time, reaching pandemic proportions (1) and also becoming more common in young adults and children (2). Currently, 382 million people suffer from diabetes, about 175 million of them remain undiagnosed (3). As a consequence of population growth, ageing, urbanization and the increasing prevalence of obesity and physical inactivity, more than half a billion people are expected to develop the disease by 2035 (3). Although type 2 diabetes may account for up to 90% of all diagnosed cases (3), in parallel, the incidence of type 1 diabetes has increased worldwide for several decades, on average 2.5–3% per year, with the most substantial increase in children younger than 5 years (4, 5). In Finland, approximately 300 000 people have been diagnosed with diabetes, and about 40 000 of them have type 1 diabetes (6). Notably, among Finnish children below the age of 15 the incidence rate of type 1 diabetes is continuously the world's highest; at the beginning of the millennium, the incidence exceeded 60 per 100 000/year (4). Due to the disconcerting trend towards younger people developing diabetes, also micro- and macrovascular complications are more likely to occur at younger ages than before, with huge economic consequences.

Diabetes is a complex chronic disease, requiring continuous medical care, with the main focus on enabling as normal a life as possible and minimizing the risks of diabetic complications (7). Nevertheless, about one-third of patients with type 1 diabetes develop diabetic nephropathy (DN), which is the leading cause of end-stage renal disease (ESRD) in the Western world, requiring dialysis or kidney transplantation (8). DN is frequently related to retinopathy and neuropathy, as well as to cardiac and cerebrovascular disease. These long-term complications are the major cause of premature mortality, morbidity, reduced quality of life and increased health care costs (9). The American Diabetes Association (ADA) provides, on a yearly basis, evidence-based guidelines for the management of diabetes (7). Also national recommendations for implementation in clinical practice exist. Despite strong evidence that intensive treatment of glycaemia, elevated blood pressure (BP) and dyslipidaemia reduces the risk of complications and improves the prognosis of patients with DN, these guidelines have not always been successfully implemented in clinical practice (7, 10–12).

In Finland, but also in the US and several European countries, the annual health care costs for diabetes represent more than 10% of health care expenditure, and these costs are to a large extent due to the escalating costs of complications (9, 13, 14). In addition, type 1 diabetes is associated with other chronic conditions such as autoimmune diseases and psychiatric disorders (15). Thus, patients with type 1 diabetes are often prescribed a variety of medications, which non-diabetic individuals do not use (16–19). The cost of prescription medication has been estimated to cover approximately one-third of the total cost of type 1 diabetes in Finland and constitutes the second largest component of the direct cost of type 1 diabetes, after the cost of hospitalization (13, 20).

As health care resources are limited, their efficient use is essential. It is obvious that treatment of type 1 diabetes patients at different stages of disease severity and duration is likely to require different levels of resources. To improve understanding of the consequences of diabetic complications, and especially the value of early diagnosis and

timely start of treatment to prevent or delay diabetic kidney disease, policymakers should be familiar with the cost structure of diabetes care. Pharmaceutical intervention plays an important role in controlling glycaemia, hypertension and other risk factors associated with progression of renal disease (7). Exploration of the changes in medication use and cost over time and identification of the main elements contributing to costs could help policymakers to focus their attention on the major cost drivers related to type 1 diabetes and its complications. This, in turn, could lead to a better utilization of available health care resources and motivate the development of strategies to reduce the incidence and progression of diabetic complications and associated costs.

Previous studies have shown that patients with diabetes take more medication than non-diabetic individuals (16-19). However, in these studies the majority of patients have had type 2 diabetes. Longitudinal studies have been rare, and the use and costs of medication have typically been evaluated only over a one-year period. Furthermore, scant data are available on type 1 diabetes patients' overall drug use and costs according to a predefined disease stage. Therefore, inadequate attention is paid to different disease severity stages in type 1 diabetes requiring different types and amounts of medication as well as other treatments, and consequently, different levels of resources.

Given this background, the aim of this thesis was to investigate the use and costs of prescription medication in patients with type 1 diabetes, stratified by severity stages of diabetic kidney disease. Similarly, we studied the implementation of the ADA guidelines by evaluating the achievement of treatment targets and how these achievements predict the prognosis of patients at different severity stages of the disease.

2 REVIEW OF THE LITERATURE

2.1 Diabetes mellitus

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycaemia secondary to inadequate production of insulin by the pancreas or a combination of insulin resistance and insulin deficiency (21). According to the World Health Organization's (WHO) criteria, diabetes is currently diagnosed based on either a fasting plasma glucose of ≥ 7.0 mmol/l in repeated measurements, a 2-h plasma glucose value of ≥ 11.1 mmol/l after an oral glucose tolerance test or a random plasma glucose value of ≥ 11.1 mmol/l in a patient who has classic symptoms (i.e. thirst, polyuria, weight loss) of diabetes (21). Recently, glycosylated haemoglobin (HbA_{1c}) with a threshold of $\geq 6.5\%$ (≥ 48 mmol/mol) has also been added as an option to diagnose diabetes (22).

2.1.1 Types of diabetes mellitus

Diabetes has traditionally been subdivided into type 1 diabetes in which autoimmune destruction of the insulin-secreting β -cells leads to absolute insulin deficiency (15) and type 2 diabetes in which insulin sensitivity and secretion are imbalanced and the increased concentration of insulin is not sufficient to meet the increased demands imposed by obesity and insulin resistance (23, 24). Although these major types of diabetes have divergent aetiology, they both seem to develop as a result of an interaction between genetic and environmental factors (15, 24). They also share the risk of developing long-term micro- and macrovascular complications. Notably, obesity, metabolic syndrome and other features of type 2 diabetes are becoming more common also in patients with type 1 diabetes, suggesting the presence of "double diabetes" (25, 26).

Over the past decades, knowledge about the pathogenesis and natural history of diabetes has grown substantially, revealing a more heterogeneous picture of the disease than merely the subdivision into type 1 and type 2 diabetes (23, 27). Type 1 diabetes (previously called juvenile or insulin-dependent diabetes mellitus) is typically diagnosed in children and young people, but it can occur at any age. By contrast, type 2 diabetes (previously called adult-onset or non-insulin-dependent diabetes mellitus) has traditionally been associated with older age, but it can also develop at any age, even during childhood. Therefore, the cut-off for age at onset (35–40 years), previously used to distinguish between type 1 and type 2 diabetes, is not decisive nowadays (23).

Although the majority of diabetes patients are currently classified as having type 1 or type 2 diabetes, other forms of diabetes also exist. The ADA has divided diabetes into four clinical classes (28). In addition to *type 1* and *type 2 diabetes*, other forms of diabetes are *gestational diabetes* and *other specific types of diabetes*, such as genetic defect in β -cell function [e.g. various forms of maturity-onset diabetes of the young (MODY), genetic defects in mitochondrial DNA, neonatal diabetes], genetic defects in insulin action, diseases of exocrine pancreas or drug- or chemical-induced diabetes. MODY is a

monogenic form of diabetes, usually inherited in an autosomal dominant pattern, characterized by lower age at onset than in type 2 diabetes, but without ketoacidosis and β -cell autoimmunity typical for type 1 diabetes (29). Gestational diabetes is diagnosed during pregnancy (about 7% of all pregnancies) and has the same pathogenesis as type 2 diabetes (28). Although it is not yet an overt diabetes, up to half of the individuals with this disorder will later develop type 2 diabetes (30).

2.1.2 Type 1 diabetes

2.1.2.1 Pathogenesis

Type 1 diabetes is a chronic autoimmune disease that develops as a consequence of gradual destruction of the insulin-producing β -cells in the pancreatic islets of Langerhans, leading to total insulin deficiency and complete dependence on exogenous insulin (15). The disease process is initiated months or even years before onset of clinical symptoms; at the time of diagnosis, about 80–90% of the β -cells have been destroyed (31). Type 1 diabetes is a polygenic disorder, and about one-half of the susceptibility is inherited through the HLA region (on chromosome 6). In addition, more than 50 non-HLA loci have been identified to affect disease susceptibility (32). However, the disorder is attributed to both genetic factors (33) and external factors that alter the immune system to trigger or sustain the development of disease (15). Putative environmental triggers include viral infections (34, 35), vaccinations (36, 37), toxins (38) and dietary factors (39). Despite investigators devoting much effort to describing the mechanisms of the disease over the past decades, it remains incompletely understood (27).

2.1.2.2 Epidemiology

The incidence of type 1 diabetes varies substantially between different countries. It is most common in Finland (~ 60 cases per 100 000/year in children below the age of 15) and Sardinia, Italy (~ 40 cases per 100 000/year), but is extremely rare in China and Venezuela (~ 0.1 cases per 100 000/year) (40). Notably, the incidence varies even between neighbouring areas; in Estonia, the incidence is less than one-third (41) and in Russian Karelia only about one-sixth of the incidence reported in Finland (42). An interesting observation is also that migrating populations adopt the incidence rate of their new country within a short time (15). For example, the prevalence of type 1 diabetes is similar among Somali and Finnish children in Helsinki, Finland (43). Globally, the incidence has been increasing during the past decades, on average 2.5–3% per year, with the steepest increase in children younger than 5 years (4, 5). The increase of the incidence rate has been too rapid to be explained by genetic factors since the gene pool changes slowly over many generations. Instead, potential hypotheses and exogenous factors have been proposed, including the hygiene hypothesis, the accelerator hypothesis, the overload hypothesis, the polio hypothesis, the hypothesis of early introduction of complex dietary

proteins and the vitamin D deficiency hypothesis (44). However, based on the most recent observations from the high-incidence-rate countries, it seems that the incidence rate has levelled off for unknown reasons (45-48).

2.1.2.3 Treatment

Obviously, the discovery of exogenous insulin in 1921 has been a revolutionary milestone in the history of diabetes: it saved the lives of patients with type 1 diabetes and became a mainstay of diabetes management. The primary goals of insulin therapy are to maintain near-normal glucose levels by mimicking the physiologic secretion of insulin by the pancreas, to avoid acute complications and to prevent long-term micro- and macrovascular complications, while enabling as normal a life as possible (49). Insulin preparations are classified according to their pharmacokinetic and pharmacodynamic profiles (50). Animal insulin, derived from cows and pigs, was the first type of insulin to be administered to humans. However, human insulin and insulin analogues have largely replaced the use of animal insulin. The first-generation synthetic human insulin was developed in the 1980s (51). More recently, insulin analogues chemically modified to either act faster (rapid-acting analogues) or slower (long-acting analogues) than human insulin provide more flexible treatment regimens with lower risk of hypoglycaemia (52).

Modern insulin therapy, recommended to most individuals with type 1 diabetes, consists of multiple daily injections or continuous subcutaneous insulin infusion (CSII) therapy (7). With the multiple daily injection regimen, long-acting basal insulin is injected once or twice a day, accompanied by a rapid-acting bolus insulin at meal-times. In CSII therapy, rapid-acting insulin is administered via insulin pump using 24-h preselected, but adjustable doses of insulin, along with patient-activated meal-time bolus doses (15). The insulin treatment regimen should be flexible to match the insulin to the diet and physical activity as well as to patient-related factors, including insulin sensitivity, stress, pubertal status and self-management skills. The amount of bolus insulin depends on the patient's pre-meal glucose concentration as well as on the carbohydrate content of the meal (7).

Recently, probably the most promising innovation for diabetes care is the development of a closed-loop system (i.e. artificial pancreas) (53). In this system, insulin pumps and continuous glucose monitors are combined with a computer algorithm. Currently, wearable smart phone-based platforms connected with insulin pumps and continuous glucose monitoring are tested in home-like conditions (54). Although abundant resources and investigations have been directed to several promising areas, such as islet-cell transplantation, pancreas transplantation, stem cells, primary and secondary disease prevention and reversal of type 1 diabetes, thus far, the results have been disappointing and have shown only limited benefit (27). Therefore, in light of present knowledge type 1 diabetes remains a disorder that cannot be prevented or cured (27).

2.2 Diabetic complications

A subset of patients with type 1 diabetes develops acute and long-term diabetic complications. These complications are not only responsible for morbidity and premature mortality (55-57), but are also the major cost drivers related to diabetes in terms of direct and productivity (previously called indirect) costs (13, 20, 58). In addition, these complications impose high intangible costs in terms of reduced quality of life, pain and suffering of afflicted individuals and their families (14, 58, 59).

Acute diabetic complications comprise hypoglycaemia, ketoacidosis and diabetic coma. Although acute complications are largely preventable, they are an important cause of early death in patients with type 1 diabetes (60, 61). Thus, acute complications are a predominating cause of death before the age of 30 years, and thereafter, cardiovascular disease (CVD) becomes the leading cause of death (62-64), accompanied frequently by other long-term complications, particularly DN (57, 65, 66).

Long-term diabetic complications, affecting multiple organ systems, can be divided into micro- and macrovascular complications. Microvascular complications affect small vessels in the kidneys (nephropathy), the retina (retinopathy) and the nerves (neuropathy). Macrovascular complications, by contrast, affect large vessels, especially coronary, cerebral and peripheral arteries. The pathways leading to micro- and macrovascular complications are complex and multifactorial, with both genetic and environmental factors playing a role. In fact, nephropathy, retinopathy and neuropathy share similar pathogenetic mechanisms in different cells and tissues (i.e. mesangial cells, microvessels and peripheral neurons) (67). Accordingly, these complications are strongly associated with each other. Also, many of the principles of care are the same.

2.2.1 Risk factors

Several non-modifiable risk factors (including age, duration of diabetes, onset age, male sex and puberty) and modifiable risk factors predict the initiation and progression of DN as well as other micro- and macrovascular complications in patients with type 1 diabetes (68-71). The main traditional modifiable risk factors are poor glycaemic control, elevated BP, smoking, lipid abnormalities and obesity (68). More recently discovered factors include chronic inflammation, advanced glycation end-products (AGEs), metabolic syndrome, physical inactivity and low exercise intensity (68). Notably, DN is more prevalent among African Americans, Asians and Native Americans than among Caucasians (72). The risk of DN and retinopathy also clusters in families, strongly suggesting involvement of genetic factors (73, 74). Moreover, a parental history of hypertension, type 2 diabetes, CVD and insulin resistance also seems to increase the risk of DN, suggesting that the genes that modulate these conditions may also be involved in the pathogenesis of DN (73, 75-77). The fact that some patients with strict glycaemic control may develop DN, while some patients with poor control do not (78), further supports the hypothesis that heritability factors may be involved.

Especially hyperglycaemia (79) and insulin resistance (80, 81) seem to play a major role in the development of atherosclerosis and microvascular complications in patients

with diabetes. In fact, many risk factors for developing DN and CVD overlap (82). Importantly, a major part of CVD in type 1 diabetes is associated with diabetic kidney disease (83). Actually, the presence of DN predicts hard CVD events, independently of hypertension, insulin resistance and dyslipidemia (84). Even a slight increase in urinary albumin excretion rate (AER) predicts atherosclerotic vascular disease (85). The risk of CVD further clusters by standard cardiovascular risk factors (such as smoking, hypertension, dyslipidaemia, obesity and family history of CVD), which for the most part are similar in diabetic and non-diabetic individuals (84, 86, 87).

2.2.2 Microvascular complications

2.2.2.1 Diabetic nephropathy (DN)

Diabetic nephropathy is the most severe and expensive late microvascular complication in patients with type 1 diabetes, especially when it leads to renal failure, necessitating dialysis or kidney transplantation (88). The risk of DN increases with duration of diabetes, with a peak incidence occurring after 15 to 20 years of diabetes; thereafter, the number of incident cases starts to decline (89-91), suggesting that a subset of patients with diabetes carries a high risk of developing DN. Moreover, DN is frequently associated with other microvascular complications and CVD (89, 92).

Diagnosis

DN is characterized by a progressive increase in proteinuria, a decline in glomerular filtration rate (GFR) and an elevated BP (93-95). The first clinically detectable manifestation of DN is often the appearance of a low, but abnormal amount of albumin in the urine (96). The classical course of DN progresses through microalbuminuria to macroalbuminuria, culminating in ESRD. Especially in Europe, the clinical diagnosis of DN is often based on the measurement of AER (96). The AER can be determined from either a 24-hour (regarded as the gold standard) or an overnight timed urine collection. Due to daily variation of AER, two out of three consecutive urine collections are needed to confirm the diagnosis. Also the measurement of the albumin-to-creatinine ratio (ACR) from a spot urine sample is suitable for screening. **Table 1** summarizes the diagnostic thresholds of different stages of DN based on these three measurements. These thresholds are, in fact, artificial but are widely accepted.

Table 1. Diagnostic thresholds for different stages of diabetic nephropathy based on three different measurements.

Diagnosis	24-hour AER	Overnight AER	ACR
Normoalbuminuria	< 30 mg/24 h	< 20 µg/min	< 2.5 mg/mmol for men < 3.5 mg/mmol for women
Microalbuminuria	≥ 30 < 300 mg/24 h	≥ 20 < 200 µg/min	≥ 2.5 < 25 mg/mmol for men ≥ 3.5 < 35 mg/mmol for women
Macroalbuminuria	≥ 300 mg/24 h	≥ 200 µg/min	≥ 25 mg for men ≥ 35 mg for women
ESRD	Dialysis or kidney transplantation		

Renal function

GFR has been most commonly used as the marker of renal function. During the course of DN also GFR begins to decrease and may finally lead to impaired renal function. Some patients, however, may follow a non-albuminuric pathway to renal impairment (97). Moreover, some patients may develop glomerular hyperfiltration (increased GFR 125–140 mL/min/1.73 m²) at early stages of diabetes. Hyperfiltration is widely regarded as a contributing factor to the development of DN (98, 99), but more recent studies have reported contradictory results (100, 101). Historically, plasma inulin has been considered the ideal filtration marker for determining GFR (102). However, the procedure for measuring inulin clearance is complex, and therefore, such a direct measurement of GFR is not feasible in routine clinical practice. Consequently, numerous equations to estimate GFR have been developed. GFR is most often estimated from serum creatinine, corrected for body mass, age, sex and ethnicity.

The most frequently used formulae are the Cockcroft–Gault equation (103), which actually estimates creatinine clearance rather than GFR, and the Modification of Diet in Renal Disease (MDRD) equation, derived from patients with chronic kidney disease (104). The Cockcroft–Gault equation is more accurate in the normal and upper-normal range of GFR, while the MDRD equation performs better in patients with chronic kidney disease (105). The more recently developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is superior to the MDRD throughout the GFR range (106). Consequently, the CKD-EPI equation has been proposed to replace the MDRD equation in routine clinical practice (107). On the basis of estimated GFR (eGFR) (mL/min/1.73 m²), renal function can be classified into five stages: normal (eGFR ≥90), mild decrease (eGFR 60–89), moderate decrease (eGFR 30–59) and severe decrease (eGFR 15–29) in renal function, as well as renal failure (eGFR < 15) (108). Albuminuria and eGFR play complementary roles in the staging and stratification of the risk of progressive diabetic chronic kidney disease. Roughly speaking, AER is a marker of the rate of progression of renal disease, while eGFR represents the advancement stage of the disease process (109). The recent clinical practice guidelines by the National Kidney Foundation classify chronic kidney disease into five stages taking into account both the presence of kidney damage and the level of kidney function (109).

Epidemiology

Without intervention, the clinical course of microalbuminuria has tended to be progressive; studies in the early 1980s demonstrated an 80% risk of progression from microalbuminuria to overt DN within 6–14 years (110, 111). Since then, the incidence has decreased considerably, suggesting that up to 30% of the patients may develop DN (112–115). Notably, more recent studies indicate an additional decline in the incidence of DN, especially in those with more recently diagnosed diabetes (92, 116, 117). By contrast, some studies have reported an unchanged incidence of DN over time (118–120). Increasing evidence has also emerged of spontaneous remission of albuminuria in patients with type 1 diabetes. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study reported that 10 years after the first occurrence of persistent microalbuminuria, up to 40% of patients reverted to normoalbuminuria, while 28% developed proteinuria and 4% ESRD (121). Remission is

more likely at the lower level of microalbuminuria and in those with improved glucose, BP and lipid control (122). Therefore, according to recent knowledge microalbuminuria is not necessarily a permanent state and it is more likely to reverse in those with optimal control of these three key factors (122). Thus, improvement of diabetes management, including better glycaemic control with self-monitoring of blood glucose and modern insulin therapy, new evidence-based treatment guidelines and the implementation of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists [also known as angiotensin receptor blockers (ARBs)], as well as other pharmaceutical interventions to control risk factors from the very beginning of the disease process may be involved (68). At the moment, however, it is unclear whether these interventions have succeeded in delaying or slowing down the progression of renal disease rather than preventing its development entirely (123).

ESRD

The cumulative incidence of ESRD has declined since the 1980s, although the risk differs substantially between study cohorts: from 1% to 13% at 20 years of diabetes duration (124-127). In Finland, the cumulative incidence of ESRD was 2.2% at 20 years and 7.7% at 30 years after diagnosis of diabetes (125). The Finnish study also showed that the cumulative incidence of ESRD was lower in more recently diagnosed cohorts of patients. Not only due to advanced prevention strategies and treatment of kidney disease, but also because excess mortality risk is attributed to chronic kidney disease, only a small proportion of the patients with type 1 diabetes will finally reach ESRD (88). In fact, premature mortality is a competing outcome to ESRD in patients with type 1 diabetes and overt nephropathy (128). The risk of death is almost three times higher in microalbuminuric patients and over nine times higher in macroalbuminuric patients than in age- and gender-matched controls (57).

2.2.2.2 Diabetic retinopathy

Diabetic retinopathy (DR) remains the most common microvascular complication of type 1 diabetes and the leading cause of visual impairment and blindness among the working age population in developed countries (129). Eventually, after 20 years of diabetes nearly all patients develop some degree of DR (130). Early signs of non-proliferative DR are microaneurysms and increased vascular permeability, followed by moderate and severe changes with haemorrhages and vascular closures (129, 131). The most severe form of the disease is proliferative DR, characterized by the growth of new blood vessels (i.e. ischaemia-induced neovascularization) in the retina and vitreous (129). Another vision-threatening complication is diabetic macular oedema, characterized by retinal thickening in the macular region. It can develop at any stage of DR (129).

The risk of proliferative DR increases with duration of diabetes and also varies considerably between different diabetes onset cohorts (92, 117, 132-134). Notably, the incidence of severe DR has declined, especially in those with more recent diabetes onset, probably due to improved control of risk factors and advances in treatment. In Finland, the cumulative incidence of severe DR (i.e. requiring laser treatment) after 20 years' duration

of diabetes was 23% and 33% in earlier cohorts (< 1975 and 1975–1979 cohorts) and 18% and 6% in later cohorts (1980–1984 and \geq 1985 cohorts) (133). Similarly, in Denmark the cumulative incidence after 20 years' duration was 31% and 30% in earlier cohorts (1965–1969 and 1979–1974) and 19% and 13% in later cohorts (1975–1984 and 1979–1984 cohorts) (92).

Notably, the occurrence of DR could be a clue to look for kidney disease since almost all patients with DN have retinopathy; however, the reverse is not necessarily true (135). Moreover, the Finnish Diabetic Nephropathy Study (FinnDiane) showed that the prevalence of proliferative DR increases with the severity of DN (136). To detect early and treatable changes, the ADA recommends screening by regular fundus photography or ophthalmoscopy be initiated in patients with type 1 diabetes at the time of puberty or within 5 years after the onset of diabetes and routine follow-up on a yearly basis (7). Over the past decades, laser photocoagulation and vitrectomy for severe forms of DR (some cases of severe non-proliferative DR, proliferative DR and macular oedema) have improved the visual prognosis of patients with severe DR (131). A new potential treatment for macular oedema is anti-vascular endothelial growth factor (VEGF) therapy, administered by intraocular injection. It has been shown to improve vision and reduce the need for laser treatment in patients with macular oedema (137).

2.2.2.3 Diabetic neuropathy

Diabetes is the most common cause of neuropathy and a major cause of morbidity owing to foot ulceration and amputation (138). Eventually, up to half of patients with diabetes will develop neuropathy during the course of their disease (139, 140). However, the assessment of the exact prevalence of neuropathy is challenging and depends on the diagnostic methods, the criteria used to define neuropathy and the study population. Diabetic neuropathy is defined by ADA as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes” (141). In fact, diabetic neuropathies are a heterogeneous group of disorders, affecting both somatic and autonomic parts of the nervous system and may vary according to the clinical manifestations, symptoms, risk factors and underlying mechanisms (71).

The most prevalent neuropathies are **diabetic peripheral neuropathy** (DPN) and diabetic autonomic neuropathy. DPN often presents first in the most distal end of the feet and spreads proximally in a length-dependent fashion. It is characterized by numbness, prickling and tingling, burning, aching, weakness, allodynia and pain (139, 140). Approximately 40–60% of patients with documented neuropathy suffer from neuropathic pain (142–144). Neuropathic pain can be severe and difficult to treat, and therefore, it is often associated with limited mobility and depression as well as with lower quality of life (145). Moreover, DPN is, together with peripheral arterial disease, the major cause of diabetic foot ulcer and lower-extremity amputations (146). About 15% of patients with diabetes may develop an ulcer during the course of their disease (147). Of note, up to 50% of patients with neuropathy may be asymptomatic, therefore being at risk of painless trauma to their feet (148). According to a European survey, the overall prevalence of DPN ranged from 10% to 25% (149). Nearly one-fifth of these patients had developed foot

ulcerations and 5% of the patients had undergone a lower-limb amputation. In Finland, the risk of amputations has decreased considerably, probably due to improved care of cardiovascular risk factors, better management of foot problems, and vascular surgical advancements (150). However, in the diabetic population the risk of a first major amputation is more than seven times higher than in the non-diabetic population (150).

Diabetic autonomic neuropathy, which may affect cardiovascular (e.g. cardiac arrhythmia, exercise intolerance, postural hypotension), gastrointestinal (e.g. gastroparesis, constipation), urogenital (e.g. urinary retention, erectile dysfunction) and sudomotor function (e.g. function of the nerves that stimulate the sweat glands), is also common in patients with diabetes (148). However, it may be asymptomatic for years and screening tests are therefore essential to detect the condition at an earlier stage. Notably, especially dysfunction of the cardiac autonomic nervous system may lead to silent myocardial ischaemia, which can be life-threatening (151). Patients with autonomic neuropathy have over two times higher risk of death than patients without autonomic neuropathy (152).

Specific treatment for the underlying nerve damage is currently not available. However, for the neuropathic pain many effective therapies exist, including medications designed to treat seizures and depression. Evidence-based guidelines have been created to assist the use of these medications for neuropathic pain (153). The treatment of neuropathic pain should be tailored to individual requirements. Duloxetine and pregabalin are current first-line treatments (140). In chronic foot ulcers, regular foot examination, including inspection, assessment of foot pulses and testing for loss of protective sensation, combined with patient education, is essential (7).

2.2.3 Macrovascular complications

Atherosclerosis in the large arteries accelerates the development of coronary artery disease, cerebrovascular disease and peripheral arterial disease in patients with diabetes (154). As described earlier, cardiovascular events are the major cause of premature morbidity and mortality (64, 155, 156) and the presence of DN further increases the risk of the events in patients with type 1 diabetes (83, 86, 155, 157, 158). Although the risk of CVD has been declining in patients with type 1 diabetes, the relative risk remains high: two- to threefold in men and three- to fivefold in women, compared with the non-diabetic population (159). Moreover, patients with DN have ten times higher risk of CVD than those without DN (83). Consequently, DN has also been shown to predict CVD mortality in patients with type 1 diabetes.

The relative risk of CVD mortality was up to 37 times higher in those with proteinuria than in the general population (157). The results from a large Finnish study showed that every percentage increase in HbA_{1c} increases CVD mortality by 52% in patients with type 1 diabetes at the age 45–64 years (160). Despite improvement in life expectancy, the overall risk of CVD mortality remains higher in patients with type 1 diabetes than in people without diabetes. Depending on the study population, the risk of CVD death may increase up to 10-fold in patients with type 1 diabetes relative to the general population (55, 156). Importantly, in the general adult population, the risk of CVD mortality is much

higher in men than in women at all ages, while in patients with type 1 diabetes the risk is equal between the sexes under the age of 40 years, suggesting a loss of gender-associated protection from CVD (156). Of note, under the age of 40 years the relative risk of mortality from coronary heart disease (CHD) was 10 times higher in men, but increased 40-fold in women, compared with the general population (156).

2.2.3.1 Coronary heart disease

The most common form of macrovascular complications is CHD, which can manifest as sudden death, myocardial infarction (MI), chest pain and heart failure. Hypertension and arterial stiffness (the surrogate markers of which are pulse pressure or pulse wave velocity) may occur early in the arteriosclerotic process and are therefore risk factors for the development of CHD (161). Treatment goals for CHD include reducing symptoms, such as chest pain, improving physical capacity and lowering the risk of blood clots (162). Besides managing the risk factors, targeted medical and revascularization procedures, including coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI), may be considered. To prevent chest pain and CVD events, β -blockers, nitroglycerides, calcium channel blockers, ACE inhibitors and antiplatelet agents are the medical therapies of particular importance (162). Notably, after the revascularization procedures the incidence of adverse events remains higher in patients with diabetes than in non-diabetic controls (163, 164).

2.2.3.2 Cerebrovascular diseases

The two major types of cerebrovascular diseases are ischaemic and haemorrhagic stroke (165). Type 1 diabetes clearly increases the risk of stroke, with a fivefold increase compared with non-diabetic subjects (166) and up to a 20-fold increase in patients aged under 50 years (167). Recently, the FinnDiane study reported that of 4083 patients 4% suffered an incident stroke between 1998 and 2010, and two-thirds of the strokes were cerebral infarctions and one-third cerebral haemorrhages (165). Notably, the incidence of both cerebral infarction and cerebral haemorrhage increased with the presence of severe retinopathy and advancing DN (165). A recent follow-up study from the UK showed that also the cerebrovascular mortality rate is higher in patients with type 1 diabetes than in the general population (168). In patients with type 1 diabetes, cerebrovascular disease accounted for 4% of all deaths under the age of 40 and 8% of deaths in those over the age of 40. Moreover, in the age group 20–39 years the risk of cerebrovascular mortality increased fivefold in men and sevenfold in women compared with the general population.

2.2.3.3 Peripheral arterial disease

Diabetes and smoking are the strongest risk factors for peripheral arterial disease (PAD) (169). PAD is characterized by narrowing or occlusion of the arteries, resulting in gradual

reduction of the blood supply to the lower extremities (170). PAD may be asymptomatic until it reaches a more severe form (169). The most common symptoms are intermittent claudication and critical limb ischaemia, causing pain in the peripheries at rest, tissue loss or gangrene (169). As mentioned earlier, PAD is a major risk factor for lower-extremity amputation, and it is also accompanied by symptomatic CVD. Studies from the early 1980s have shown that the prevalence of PAD is higher in patients with diabetes (170). However, only limited data on PAD exist in patients with type 1 diabetes. The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study examined the incidence of PAD in 586 patients with type 1 diabetes as well as factors related to PAD. They found that the incidence was 13 events/1000 person-years (171). During the 10-year follow-up, they observed 70 PAD events, 40 of which were claudication, followed by 13 amputations, 10 ulcers and 7 combined events. Duration of diabetes, HbA_{1c}, hypertension, heart rate and AER were the factors independently predicting the occurrence of PAD.

Major goals for the treatment of PAD are management of symptoms and prevention of CVD mortality by stopping the progression of atherosclerosis (170, 172). In addition to lifestyle and risk factor modification, exercise therapy and antiplatelet agents, usually aspirin or clopidogrel, improve walking distance, reduce the need for vascular interventions and improve patency rates after vascular interventions (170). Some patients may benefit from the use of pentoxifylline, which reduces blood viscosity and improves erythrocyte flexibility (172). Moreover, timely referral for a revascularization procedure might improve the outcomes of PAD (170). The choice of the procedure depends on the site and extent of disease, distal run-off and surgical risk due to associated CVD (170). Proximal, short segment disease in the iliac or femoral segments is an indication for percutaneous transluminal balloon angioplasty (PCTA) with or without stenting, while in more distal disease in the popliteal and tibial arteries, surgical bypass grafting may be better (170, 173). If vascular procedures are contraindicated, hyperbaric oxygen therapy may be considered in some cases (173).

2.2.4 Prevention and treatment

Importantly, most of the micro- and macrovascular complications could be prevented, delayed or reduced with early implementation of preventive and therapeutic strategies, reducing the economic burden of diabetes and its complications (174, 175). Multifactorial therapeutic approaches are the most effective in preventing the development of diabetic complications, and halting the progression of chronic kidney disease. Therefore, prevention/treatment is aimed at aggressive treatment of glycaemia, elevated BP and dyslipidaemia and smoking cessation. Previous studies have shown that the prevalence of obesity has risen in patients with type 1 diabetes, and metabolic syndrome is also a common finding, especially among those with DN and poor glycaemic control (25, 176). Therefore, behaviour modification, such as weight loss, exercise, dietary changes and reduction in alcohol use, as well as assessment of mood disturbances should be included in multifactorial strategies (177).

2.2.4.1 Glycaemic control

Hyperglycaemia plays a major role in the initiation of all vascular complications through many metabolic and structural changes, including the formation of AGEs, oxidative stress, protein kinase C activation and abnormal stimulation of haemodynamic regulation systems (i.e. the renin-angiotensin system) (178, 179). These changes contribute to the damage of target organs.

The landmark DCCT study established the effectiveness of optimal glucose control in reducing the risk of the development and progression of DN, DR and neuropathy (180). The EDIC follow-up study further reinforced the concept by showing the long-lasting benefits of intensive therapy (known as metabolic memory); intensive insulin therapy reduced the risk of microalbuminuria by 39% and the risk of albuminuria by 54% (181). Participants from the intensive therapy group continued to experience lower rates of incident microalbuminuria and macroalbuminuria, with risk reductions of 59% and 84%, respectively (182). The DCCT showed that intensive glycaemic control reduced the incidence of DR by 76% and slowed the progression of existing DR by 54% (183). The occurrence of clinical neuropathy diminished by 60% with intensive insulin therapy compared with conventional therapy (56). A long-term beneficial influence of early intensive glycaemic control was recently shown, translating into a lower subsequent risk of DPN and cardiovascular autonomic neuropathy (CAN), as the EDIC follow-up study demonstrated that the prevalence of confirmed DPN at years 13/14 was 25% in those with intensive treatment therapy and 35% in those with conventional therapy during the DCCT (184). The corresponding numbers for CAN were 29% and 35%. Thus, better glycaemic control in the past translated into a lower risk several years later.

The DCCT/EDIC study finally demonstrated that intensive treatment during the 17 years of prospective analysis was associated with a 42% risk reduction in all CVD events and a 57% reduction in the risk of non-fatal MI, stroke, or death from CVD (185). Notably, the large variability in the HbA_{1c} also predicts the progression of renal disease and CVD events in patients with type 1 diabetes (186). These findings highlight the importance of intensive insulin therapy implemented early in the course of diabetes in order to achieve a blood glucose level as near to normal as possible, but without risk of adverse events.

Insulin analogues and better delivery systems combined with intensive glucose monitoring are key elements to achieve the desired glycaemic goals. Insulin analogues have been associated with a lower risk of hypoglycaemia (187). Therefore, insulin analogues delivered either by multiple daily injections or via CSII are recommended for most individuals with type 1 diabetes (7). Nowadays, sensor-augmented insulin pump therapy with a threshold-suspend feature is also making substantial progress in diabetes care (27). A trial in which a sensor-augmented pump (insulin pump and continuous glucose monitor together) has been compared with multiple daily injection therapy showed significant improvement in HbA_{1c} reduction with less hypoglycaemia in the sensor-augmented cohort (188). These pumps and their supplies are, however, expensive. Currently, limited data exist on the impact of these pumps on clinical results and costs over time. By modelling the long-term effects of these modern insulin pumps, some investigators have estimated a large reduction in future complications of the disease, and

consequently, on the spending needed to treat such complications (189). Based on recent ADA guidelines, these pumps should be considered at least for patients with frequent nocturnal hypoglycaemia and/or hypoglycaemia unawareness (7).

2.2.4.2 Blood pressure (BP) control

Hypertension is a major risk factor for microvascular complications and CVD (86, 190, 191). High BP both parallels (i.e. BP rises along with the increase in AER) and precedes (i.e. high BP accelerates the loss of kidney function) the worsening of diabetic kidney disease in patients with type 1 diabetes (93-95, 192). Typically, hypertension manifests when the patient develops microalbuminuria (193). Intensive treatment of elevated BP reduces the risk of microvascular complications and CVD, and improves the prognosis of patients with DN, especially combined with the use of agents acting on the renin-angiotensin-aldosterone system (RAAS), which are highly effective in slowing the progression of renal disease (194-197). Beneficial effects have also been demonstrated in slowing the progression of DR (198, 199).

The first-line drugs of choice include ACE inhibitors or ARBs, which have repeatedly been shown to have a beneficial effect on albuminuria and renal function, beyond the BP-lowering effect (200). ACE inhibitors or ARBs are recommended also for the treatment of microalbuminuric normotensive patients. Most patients with hypertension might require multiple-drug therapy to reach the BP treatment goals (201). Diuretics, calcium channel blockers and β -blockers are recommended as additional therapy to achieve a further lowering of BP, or alternate therapy if ACE inhibitors or ARBs are not tolerated (7). In addition, patients with elevated BP should, if necessary, be advised on lifestyle changes, including a healthy diet, weight control, reduction of sodium intake, moderate alcohol intake, smoking cessation and increased physical activity (7).

2.2.4.3 Lipid control

Dyslipidaemia is not only a significant risk factor for CVD in patients with type 1 diabetes (202, 203), but also a major independent risk factor for the development of chronic kidney disease (204). In fact, dyslipidaemia plays a role in the progression of DN (205). Several lipid abnormalities, such as increased triacylglycerol and low-density lipoprotein cholesterol (LDL-C) or decreased high-density lipoprotein cholesterol (HDL-C) levels, have frequently been observed in patients with poorly controlled type 1 diabetes or with DN (206, 207). Patients with optimally controlled type 1 diabetes, without diabetic kidney disease, may have a normal or even elevated HDL-C concentration. A recent FinnDiane study demonstrated that different lipid abnormalities may also be involved at different stages of DN. High triacylglycerol, apolipoprotein (Apo)B, ApoA-II and HDL₃-cholesterol predicted incident microalbuminuria, while progression of macroalbuminuria was predicted by high triacylglycerol and ApoB (205). A previous study demonstrated that different sizes of very-low-density lipoprotein (VLDL) particles may be associated with the progression of DN; cholesterol in the large VLDL particles was associated with

incident albuminuria, whereas cholesterol in the medium-sized VLDL particles was associated with microalbuminuria (208). Although these qualitative lipid changes might have an even greater role than the quantity of the major lipoproteins in the development of CVD or DN, their features are still not fully understood (68, 209). Undoubtedly, to reduce the progression of DN and CVD it is important to pay attention to lipid abnormalities in patients with type 1 diabetes.

Based on the ADA guidelines, the goals of LDL-C < 2.6 mmol/L (< 100 mg/dL), triacylglycerol < 1.7 mmol/L (< 150 mg/dL) and HDL-C > 1.0 mmol/L (> 40 mg/dL) and > 1.3 mmol/L (> 50 mg/dL) in men and women, respectively, are desirable in most adult patients with diabetes (7). In clinical practice, LDL-C is usually estimated indirectly with the Friedewald equation (210). The Friedewald equation provides an adequate estimate of LDL-C for most fasting specimens, but is known to be less reliable as triacylglycerol concentration increases. The Friedewald equation should not be used if plasma triacylglycerol concentration exceeds 4.52 mmol/L (400 mg/dL) (211).

Statins are the first choice of lipid-lowering drugs in patients with diabetes (7, 212). A previous prospective large-scale meta-analysis of 71 370 non-diabetic individuals and 18 686 persons with diabetes from 14 randomized trials has demonstrated that treatment with statins significantly reduced the risk of CHD and mortality (213). They reported a 20% reduction in major vascular events per mmol/L reduction in LDL-C in people with and without diabetes. Therefore, in addition to lifestyle modification, including reduction of saturated fat, trans fat and cholesterol intake, statin therapy should be considered if LDL-C remains above 2.6 mmol/L, or in those with multiple CVD risk factors (7). Moreover, in those with overt CVD or aged over 40 years and with other CVD risk factors, pharmacological treatment should be added, regardless of baseline lipid levels. For those with overt CVD, a more stringent LDL-C target of < 1.8 mmol/L (< 70 mg/dL) is desirable (7). If statins are contra-indicated (due to cholestasis and active liver disease) or not tolerated (due to adverse effects on muscles, such as myopathy), alternative therapies, e.g. fibrates or ezetimibe, may be used. In general, fibrates have a better effect on triacylglycerol levels than on LDL-C and HDL-C levels, and therefore, they are more frequently used in those with elevated triacylglycerol (214).

2.2.4.4 Smoking cessation

Several studies have shown that cigarette smoking is associated with increased risk of onset and progression of DN (215, 216), as well as with other microvascular complications (217). Moreover, smoking is a leading cause of CVD (218), and indeed, patients with type 1 diabetes who are smokers are undoubtedly at risk. It is important that smokers be encouraged to stop smoking. Similarly, the risks of smoking should be disclosed to type 1 diabetes patients as early as possible.

2.2.4.5 Antiplatelet therapy

Aspirin (i.e. acetylsalicylic acid) has been shown to be effective in reducing CVD events in high-risk patients with previous MI or stroke (secondary prevention) (219). Hence, long-term low-dose aspirin therapy or clopidogrel (if aspirin allergy) are recommended for those with a history of CVD, including MI, vascular bypass procedure, stroke, peripheral vascular disease and claudication (7, 220). Aspirin as a primary prevention is recommended only for those patients with type 1 diabetes who have an increased CVD risk (10-year risk > 10%), mostly men aged > 50 years or women aged > 60 years who have at least one additional CVD risk factor (i.e. family history of CVD, hypertension, hyperlipidaemia, smoking or albuminuria). It is not, however, recommended for patients with low CVD risk (10-year risk <5% and no additional risk factors) since potential adverse effects, such as gastrointestinal bleeding, are likely to outweigh the potential benefits (7, 220, 221).

Moreover, to prevent thrombosis and thromboembolism, oral anticoagulants (the most common of which is warfarin) are often prescribed for patients with atrial fibrillation or pulmonary embolism or after artificial heart valve surgery or orthopaedic procedures (222).

2.2.4.6 Other treatment options

Especially patients characterized by macroalbuminuria or renal failure are likely to display multiple co-morbidities, including cardiovascular disease, secondary hyperparathyroidism, electrolyte disturbances and anaemia, as well as bone and mineral metabolism disorders (BMDs), requiring multiple pharmacological therapies. Anaemia with erythropoietin (EPO) deficiency and BMD are common findings in patients with renal failure (223, 224). However, these disorders often occur at an earlier stage in the course of diabetic renal disease than in other forms of kidney diseases (223, 225).

Chronic anaemia stresses the heart by increasing cardiac output, volume overload and pulse rate and contributes to left ventricular hypertrophy and diastolic dysfunction (226), and thus, is a risk factor for CHD (227). Patients with renal anaemia can be treated with injections of erythrocyte stimulating agents (ESA) (e.g. EPO, darbepoetin alfa). The treatment with ESA may improve the patient's quality of life and reduce the need for red blood cell transfusion. However, excess correction of the anaemia should be avoided due to the risk of adverse events (i.e. death, serious adverse cardiovascular reactions, stroke) (228). To optimize responsiveness to ESA, also iron stores should be replete by administration of iron either orally or intravenously (229).

BMDs may be reflected by the following markers, either solely or in combination: abnormalities of calcium, phosphorus, parathyroid hormone (PTH) and vitamin D metabolism, as well as by abnormalities of bone turnover, mineralization, volume, growth and strength, and vascular or soft tissue calcification (224, 230). Appropriate management of bone disease is complex and requires not only modification of the diet, but may also be treated by phosphorus binders (e.g. calcium carbonate, lanthanum carbonate, sevelamer), vitamin D analogues and calcimimetic agents (230).

Renal failure requires either haemodialysis or peritoneal dialysis, often followed by kidney transplantation. Occasionally, the kidney is transplanted together with the pancreas in patients with type 1 diabetes. Compared with dialysis, kidney transplantation prolongs survival, improves quality of life and is more cost-effective (231-233). In order to prevent rejection, all patients with an organ transplant require life-long use of immunosuppressive therapy. Typically, combinations of two to three drugs with different mechanisms of action are used to achieve efficacy with limited toxicity (234, 235).

2.3 Other co-morbidities

In addition to diabetic complications, type 1 diabetes is frequently associated with other chronic conditions such as other autoimmune diseases and psychiatric disorders. These co-existing co-morbidities greatly increase the complexity of diabetes care, especially related to a large number of prevalent symptoms and polypharmacy, as well as the use of health care service and health care costs (236).

2.3.1 Other autoimmune diseases

Patients with type 1 diabetes are more likely to have other autoimmune diseases that are characterized by the production of organ-specific autoantibodies, including autoimmune thyroid disease, coeliac disease and Addison's disease (15, 237). These autoimmune diseases tend to co-exist not only in type 1 diabetes individuals, but also in family members, implying a shared aetiology (238). Also some other organ-specific autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis and asthma, occur more often in patients with type 1 diabetes than in healthy controls. No cure exists for multiple sclerosis, rheumatoid arthritis or asthma. However, early diagnosis and effective pharmacological treatment are critical in slowing the progression of the disease and controlling symptoms.

The most common disorder is **autoimmune thyroid disease**, affecting up to 30% of patients with type 1 diabetes (239). Up to one-quarter of newly diagnosed type 1 diabetes patients have thyroid autoantibodies (240-243), which predict a thyroid dysfunction, either hypothyroidism or less commonly hyperthyroidism with or without an enlarged thyroid gland (called goitre) (242). Hypothyroidism increases the risk of hypoglycaemia (244) and also retards the linear growth of children (245). Patients with hypothyroidism require thyroid hormone replacement therapy (i.e. levothyroxine sodium) (246). Hyperthyroidism causes fluctuation in blood glucose, which may lead to deterioration of metabolic control (7). Treatment consists of antithyroid medications (e.g. carbimazole) or thyroid ablation with either radioactive iodine therapy or thyroidectomy (247). A current guideline from the ADA recommends screening of children with type 1 diabetes for thyroid autoantibodies soon after diagnosis, as well as measuring thyroid-stimulating hormone (TSH) concentration after metabolic control's stabilization at onset of diabetes. If TSH is normal, rechecking should be done every 1-2 years or earlier if the patient develops

symptoms of thyroid dysfunction or has an abnormal growth rate or unusual glycaemic variation (7).

Coeliac disease (CD) occurs with increased frequency in patients with type 1 diabetes, with a range between 1% and 16% (248-251). CD is characterized by intolerance to dietary gluten. The gluten-triggered autoimmunity damages the small bowel mucosa, leading to chronic malabsorption, multiple vitamin deficiencies and poor growth (252). Moreover, in patients with type 1 diabetes variable absorption of carbohydrates can cause blood glucose fluctuation, and malabsorption of carbohydrates increases the risk of hypoglycaemia. A gluten-free diet reduces the symptoms and the rates of hypoglycaemia (253). Current ADA guidelines recommend the measurement of autoantibodies soon after the diagnosis of diabetes and in those with a family history or symptoms of CD (7). Moreover, subjects with positive antibodies should have an intestinal biopsy to confirm the diagnosis. Many companies manufacture gluten-free products, which are more expensive than so-called usual products. In Finland, patients with CD (doctor's certificate required) can apply for diet reimbursement from the Social Insurance Institution of Finland (i.e. Kela) (23.60 €/month in 2014) (www.kela.fi).

Addison's disease causes destruction of the adrenal gland, resulting in primary adrenal insufficiency. Compared with the general population, Addison's disease is more common in patients with type 1 diabetes, even though it occurs in only 0.5% of them (237). Patients with symptomatic adrenal insufficiency should be treated with hydrocortisone and fludrocortisone as a substitute for aldosterone (254).

Multiple sclerosis (MS) affects nerves in the brain and spinal cord, with focal lymphocytic infiltration leading to damage of myelin and axons, causing loss of muscle control, vision and sensation (255). The relative risk of MS has been reported to be three- to fivefold in patients with type 1 diabetes (256-258). The pharmacological treatment of MS depends on the symptoms and severity stages of the disease process. The first-line immunomodulating drugs of choice are interferon- β or glatiramer acetate (Käypä Hoito 20.12.2012). Other treatment options, such as natalizumab or fingolimod, may be considered as second-line therapies. All of these treatments are expensive and their efficacy varies with the stage reached in the disease process (255).

Rheumatoid arthritis (RA) is characterized by persistent synovitis and systemic inflammation of the joints, which can permanently damage the joints, cartilage and bone (259). Only a few small studies have assessed the prevalence of RA among type 1 diabetes patients. A Finnish study showed a two times higher risk of type 1 diabetes in patients with juvenile idiopathic arthritis, while a study from the US reported a sixfold higher risk than in the general population (260, 261). The treatment of RA consists of a combination therapy, including disease-modifying anti-rheumatic drugs, such as methotrexate, as well as non-steroidal anti-inflammatory drugs and steroids (259). Moreover, the development of new biologic agents has expanded the treatment possibilities (259).

Asthma is an inflammatory disease of the airways that is characterized by recurrent episodes of bronchial obstruction (262). An increasing prevalence of asthma has been reported during the past decades in many countries (263). Also a positive association between the occurrence of type 1 diabetes and symptoms of asthma has been observed in Europe and elsewhere (264). Asthma is usually treated with inhaled corticosteroids with or

without a long-acting beta antagonist, as well as with quick-relief medication (such as short-acting beta antagonists or oral/intravenous corticosteroids) (262).

2.3.2 Psychiatric disorders

Depression, anxiety, diabetes-related distress, eating disorders and other mental health symptoms are common in patients with diabetes and may negatively affect the overall management of diabetes (7). These co-morbid psychiatric disorders may contribute to poor self-care and adherence to the medication regimen, reduce the quality of life and produce higher rates of morbidity and mortality, consequently increasing health care costs (265-269). According to a meta-analysis, the prevalence of depression was almost four times higher in patients with type 1 diabetes than in non-diabetic controls (12% vs. 3.2%) (270). The prevalence was even higher when the symptoms were combined with the use of antidepressant medications (271). Routine assessment of the patient's psychological and social situation is therefore essential as part of the management of diabetes; referral to appropriate services (such as a mental health specialist) should be considered, when necessary (7). Depending on the form and severity of the psychiatric disorders, the treatment usually consists of a combination of pharmacotherapy (e.g. antidepressants, antipsychotics, anxiolytics) and psychological interventions (272).

2.4 Factors affecting costs of medication

As described above, insulin therapy is the most essential part of the care of patients with type 1 diabetes. Moreover, pharmaceutical interventions play an important role in controlling hypertension and other risk factors as well as in treating related co-morbidities. This section provides an overview of the Finnish health care system and structural features affecting the prices of medications. These factors have an impact on medication utilization and costs in patients with type 1 diabetes.

2.4.1 Overview of the Finnish health care system

All residents in Finland have a right to health care and social services. At present, the Finnish health care system is decentralized largely to the municipalities. Local authorities have the responsibility of organizing the delivery of public health services, including primary, specialized and long-term care. Primary health care can be arranged at each municipality independently or at the local government joint service areas (with at least 20 000 inhabitants). In general, local authorities can decide the scale, scope and model of municipal services within the limits of legislation. To fulfil its responsibility for organizing specialized care, each municipality must belong to one of the 20 hospital districts. Hospital districts provide specialized medical care services that cannot be incorporated into primary health care. Access to specialized care requires referral from

either a municipal or a private physician. Moreover, each hospital district belongs to one of five university catchment areas that co-ordinate the provision of specialized medical care and provide highly specialized medical services. In addition to the public sector, private health care providers (i.e. enterprises or non-governmental organizations) can sell their services to local authorities, joint municipal authorities or directly to clients. Public health services are financed by the municipalities out of local taxation and user fees. Regional and university hospitals are financed by federations of participating municipalities. The State also makes transfer payments to local authorities. The amount depends on the size of the population, the population structure and morbidity. (273, 274)

Currently, the system is undergoing a thorough reform to ensure meeting the main goals of guaranteeing equal services countrywide and implementing a cost-effective and high-impact service structure (275). The arrangement and provision of services will be treated as separate entities. After the reform, the responsibility for organizing the services will rest with five social welfare and health care regions, while the municipalities and joint municipal authorities will continue to provide services by themselves or by procuring services from organizations and companies (275).

In Finland, children with type 1 diabetes are treated mostly in paediatric clinics in central or some local hospitals. Depending on the areas of Finland, adults with type 1 diabetes either have regular visits to specialized outpatient clinics or see their general practitioner at health centres. In most cases, type 2 diabetes care is organized by the health centres or the occupational health care system. Diabetes drugs and blood glucose self-monitoring devices are available free of charge or at low cost to all diabetes patients (276).

2.4.2 Finnish National Health Insurance

The statutory Finnish National Health Insurance (NHI) covers all permanent residents in Finland as part of social security. It is co-ordinated by the Social Insurance Institution, which is an independent body under public law and falls under the direct supervision of the Finnish Parliament. Health insurance is divided into two pools: earned income insurance and medical care insurance. Earned income insurance constitutes sickness, parenthood and rehabilitation allowances and part of the occupational health care. Medical care insurance involves reimbursements for medication expenses and private sector health care services (including dental care, doctors' fees, examination and treatment charges), as well as travel expenses and rehabilitation services according to the statutory reimbursement rate. Earned income insurance is financed by a statutory contribution from employees and employers (calculated as a fixed proportion of employee wages), and medical care insurance equally by the insured (deducted from income, pension and other benefits) and the State. (274)

2.4.3 Drug reimbursement system

Of the total sales of pharmaceuticals, approximately three-quarters are prescription-only medications used in outpatient care, about 10% over-the-counter medications and about

15% medications used in inpatient care (277-279). The NHI offers a three-level reimbursement system for medication prescribed in outpatient care in order to promote the availability of high-quality, cost-effective and reasonably priced medications to all residents in Finland. The system was established in Finland in 1964 and is currently based on the Health Insurance Act 1224/2004 (279). The system consists of the Basic Refund Category (35% of the price in 2014) and the Lower (65% of the price in 2014) and Higher (100% of the price in 2014, a 3.00 € co-payment is charged for each medicine purchased at one time) Special Refund Categories (Health Insurance Act 1224/2004, amended by Act 622/2012) (277, 279). These categories are set according to the severity of the disease and the necessity of drug treatment. The Lower Special Refund Category consists of 10 diseases that are serious and chronic, e.g. hypertension, asthma or CHD. The Higher Special Refund Category includes 34 serious and chronic diseases where drug treatment is necessary for patients and where the drug restores or replaces normal bodily functions, e.g. diabetes, malignant diseases or post-transplant conditions (279). Moreover, when out-of-pocket medicine expenses (the non-reimbursable sum) in a calendar year exceed the established limit (610 € in 2014, www.kela.fi), the exceeding portion is reimbursed in full, and thereafter, only a 1.50 € co-payment is charged for each medicine purchased at one time, as well as any proportion of the medication's price exceeding the reference price.

Notably, medications administered in hospitals or in other institutionalized care are not included in the reimbursement system. Pharmaceutical companies negotiate directly with the hospitals to determine the prices of medications (273). Medications administered in hospitals are covered by the hospital budget (financed by the municipalities, which transfer funds to hospitals). Consequently, the cost of bed-days in hospitals includes medications administered during the hospital stay.

2.4.4 Marketing authorization and price of medicinal products

A medicinal product must have a marketing authorization before it can be placed on the market and made available to consumers (279). Marketing authorizations are granted either by the European Commission (handled by the European Medicines Agency, EMA) or by the Finnish Medicines Agency (FIMEA) (279). In principle, pharmaceutical companies can set their wholesale prices freely. However, the costs of medicinal products are reimbursed only when the holder of the marketing authorization has applied for reimbursement. The Pharmaceuticals Pricing Board (PPB, HILA) approves the reimbursement status of the medicine and confirms its reasonable wholesale price (279).

The PPB, operating under the Ministry for Social Affairs and Health, decides which medicinal products (generics, parallel trade and patented drugs) are to be included in the reimbursement system and confirms their wholesale prices and reimbursement rates within 180 days of receipt of the application. The PPB also requests the Social Insurance Institution to submit an opinion on whether the criteria for granting reimbursement status and for a reasonable price are fulfilled, as well as an opinion on the budget impact from the NHI. A confirmed reasonable wholesale price is the maximum price at which the product may be sold to pharmacies and hospitals. The PPB can also target and limit the payment of the Basic Refund of certain drugs to a precisely defined diagnosis and severity

stages, such as drugs used in the treatment of multiple sclerosis, certain rheumatoid diseases or erectile dysfunction. Moreover, the Board makes decisions related to the reference price system (i.e. reference price groups, reference prices, products in each group). (279)

The PPB's decisions are based on an application submitted by the holder of the marketing authorization. The application must include an assessment of the product's therapeutic value, necessity and economic efficiency as well as sales and usage estimates. Moreover, it must include a description of the position of the drug among other equivalent drug treatments, the product's patent status and prices in other European Economic Area member states. If the product contains a new active substance, a health economic evaluation should be included. In practice, a medicinal product must hold the basic reimbursement status for at least two years until it is eligible for special reimbursement status. (279)

The retail price of the drug (total cost of drug and the sum from which the reimbursement is calculated) includes the share of the manufacturer and wholesaler, the pharmacy margin, the tax-like pharmacy fee and the Value Added Tax (VAT) based on the drug tariff issued by the Government which all pharmacies must follow. **Table 2** shows the calculation formula for retail prices of prescription medications. The retail price is the same in all pharmacies in Finland.

Table 2. Calculation formula for retail prices of prescription medications based on the Medicinal Tariff Decree 1087/2002 and the new Decree on Pharmaceutical Tariff 713/2013 valid from 1.1.2014 (in parentheses).

Wholesale price (€)	Retail price
0–9.25	1.5 x wholesale price + 0.50 € (1.45 x wholesale price) + VAT [†]
9.26–46.25	1.4 x wholesale price + 1.43 € (1.35 x wholesale price + 0.92 €) + VAT
46.26–100.91	1.3 x wholesale price + 6.05 € (1.25 x wholesale price + 5.54 €) + VAT
100.92–420.47	1.2 x wholesale price + 16.15 € (1.15 x wholesale price + 15.63 €) + VAT
> 420.47	1.125 x wholesale price + 47.68 € (1.1 x wholesale price + 36.65 €) + VAT
+ The handling fee of each medicinal product 0.39 € (2.17 €) [†] Value Added Tax	

2.4.5 General trends in pharmaceutical costs

Pharmaceutical expenditure has increased rapidly in Finland in the past two decades and has been one of the fastest-growing components of the total health expenditure (273). Although there is a wide variation among countries, the growth in pharmaceutical spending is a worldwide phenomenon. Reasons for increasing pharmaceutical costs include ageing of the population, introduction of new and relatively expensive drugs, increasing number and prevalence of diseases susceptible to drug treatment, extension of drug indications (i.e. disease prevention and treatment of less significant ailments and symptoms) and increasing overall volume of pharmaceuticals (278). In Finland, the wholesale prices of drugs are about the average in Europe, while due to the VAT and

pharmacy fee, the retail prices are above the average (280). The patients' co-payments for reimbursable drugs have increased over time.

To promote cost-effective prescription strategies and restrain growth in pharmaceutical spending, several legislative measures to regulate pricing and reimbursement procedures have been implemented in Finland as well as in other countries over the past decade. Despite the continuous increasing trend of medication consumption and pharmaceutical spending, these measures have, at least temporarily, restrained the increasing trend in the sales of medications and reimbursement expenditure (**Figure 1**). While in the 1990s and early 2000s the real costs (deflated with cost of living index) of prescription medication used in outpatient care increased on average by 9% from the previous year, the annual growth slowed in 2002–2011, being on average about 0.7% (281).

In 2009, when the reference price system was introduced and generic substitution was extended to cover drugs holding an analogous process patent, the total sales of pharmaceuticals decreased by 1.3% from the previous year. Notably, for the first time in Finnish reimbursement history, also reimbursement payments decreased by 1.6% from the previous year in 2010 (282). However, these numbers demonstrate only temporal trends since the sales of pharmaceuticals as well as reimbursement expenditure have started to grow again in 2011.

The following section provides information about some legislative measures that have directly or indirectly affected the general development of medication costs in Finland. The main reforms and changes to regulate pricing and reimbursement procedures are presented in **Table 3**.

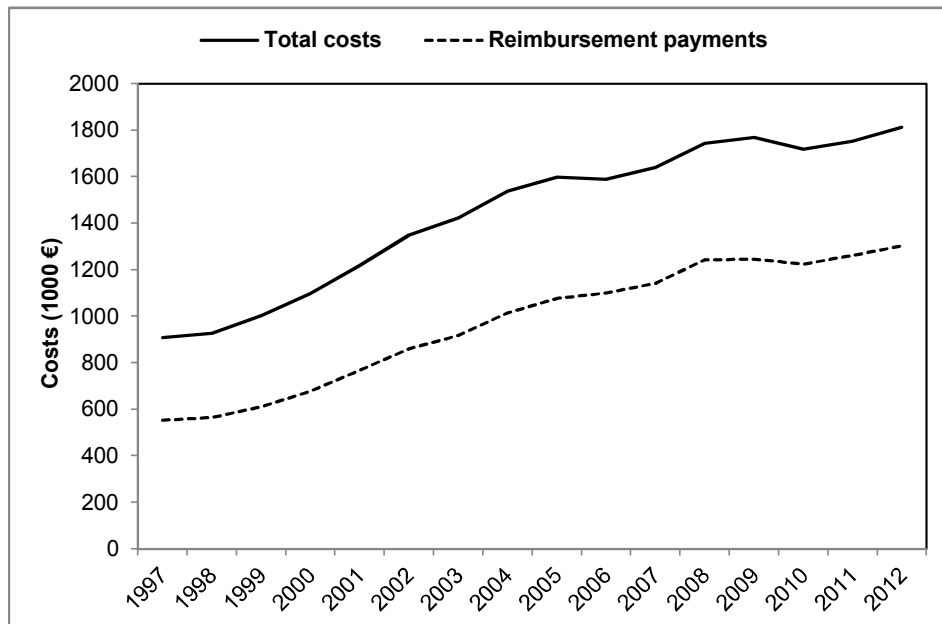


Figure 1. Observed costs (at current prices) of prescription medication and their reimbursement in 1997–2012 (277, 279).

2.4.6 Drug cost containment by legislative measures

In 1995, turnover tax for pharmaceuticals was replaced by a VAT of 12%. This change increased the retail prices of medicines by about 7% (283, 284). In 1998, the VAT applicable for pharmaceuticals was reduced from 12% to 8%. At the same time, the medicine tariff affecting pharmacies' sales margins was changed in a more degressive (gradually decreasing rate in sums below a certain amount) direction, and prices of stockpiled medicines decreased since the compulsory stockpiling surcharge was abolished. Therefore, a slight plateau was observed in the medication costs during that year. However, in response to the economic crisis, the VAT was again increased to 9% in 2010 and finally to 10% in 2013. At the same time, the reimbursement rates in the Basic and Special Refund Categories were decreased. However, the threshold of the patient's out-of-pocket medicine expenses was also decreased, benefitting especially those requiring multiple medications (www.kela.fi).

In 2006, the fixed deductible sum per purchased medication was given up. Instead, a certain percentage of the drug price is reimbursed on the basis of the relevant reimbursement category. However, the average reimbursement rate remained essentially the same since the Basic Refund Category was decreased from 50% to 42% and the Lower Special Refund Category from 75% to 72%. The Higher Refund Category (100%) was not changed, but a 5.00 € co-payment payable per purchase was replaced with a 3.00 € co-payment charged for each medicine purchased at one time. As a consequence of this reform, the number of patients receiving reimbursement of medication costs increased by about 10% in 2006 (285). However, also the wholesale prices were cut by 5%, and the total costs of prescription medicines decreased slightly, but only temporarily, from the previous year for the first time (285). The latest wholesale price cut was implemented in 2013, as the wholesale prices of medicines outside the reference price system were decreased by 5%. At the beginning of 2014, the new medicine tariff was established (Medicinal Tariff Decree 713/2013) in which the retail prices of the most expensive drugs were decreased and the least expensive drug prices were increased. Also the handling fee was increased.

Generic substitution was adopted in April 2003. This enables a prescribed original medicinal product to be replaced by a less expensive generic product with equivalency in terms of active ingredient strength, dissolution and bioavailability, unless the doctor or the buyer declines the replacement (286, 287). The list of approved substitutable drugs is maintained by the FIMEA, and the price corridor for different groups of substitutable drugs is updated four times a year, following price notifications submitted from the marketing authorization holders. During the first year of generic substitution the average price of substitutable drugs decreased by more than 10%. Over half of the savings were generated by lipid-lowering drugs and antidepressants (286). Despite the fact that the generic drugs are less expensive than the branded ones, the generic substitution has also fostered competition between the original manufacturers and the manufacturers of generic substitutes. Of note, following generic substitution and price competition, the consumption of cardiovascular drugs has increased by 10%, but their sales value has increased by only 1% (288).

Table 3. Main reforms and changes in the reimbursement system and prices of drugs between 1994 and 2013 in Finland (www.kela.fi) (279, 283-285).

Year	Reforms and changes	Main objectives of the reforms
1994	<ul style="list-style-type: none"> The PPB¹ responsible for setting wholesale prices 	➤ To control prices of drugs
1995	<ul style="list-style-type: none"> Turnover tax replaced by VAT² of 12% 	➤ To increase government revenues
1996	<ul style="list-style-type: none"> Generic substitution³ was replaced by generic prescribing 	➤ To reduce pharmaceutical spending
1998	<ul style="list-style-type: none"> VAT reduced to 8% Compulsory stockpiling surcharge abolished Pharmacies' margin more degressive 	➤ To control prices of drugs
2003	<ul style="list-style-type: none"> Generic substitution introduced 	<ul style="list-style-type: none"> ➤ To reduce pharmaceutical spending ➤ To increase competition between pharmaceutical companies
2006	<ul style="list-style-type: none"> Fixed deductible sum per purchased drug abolished and Refund Categories changed Basic: from 50% (the fixed deductible sum 10 €) to 42% Special Lower from 75% (the fixed deductible sum of 5 €) to 72% Special Higher from 100% (+5 €/purchase) to 100% +3.00 €/drug Wholesale prices cut by 5% Biosimilars entered the EU market 	<ul style="list-style-type: none"> ➤ To reduce reimbursement payments ➤ To reduce pharmaceutical spending
2009	<ul style="list-style-type: none"> Reference price system introduced Generic substitution extended to cover drugs holding an analogous process patent 	<ul style="list-style-type: none"> ➤ To reduce pharmaceutical spending ➤ To increase competition between pharmaceutical companies
2010	<ul style="list-style-type: none"> VAT increased to 9% 	➤ To increase government revenues
2013	<ul style="list-style-type: none"> Refund Categories decreased Basic from 42% to 35% Special Lower from 72% to 65% Threshold of the patient's out-of-pocket medicine expenses decreased VAT increased to 10% Wholesale prices of drugs outside the reference price system cut by 5%. 	<ul style="list-style-type: none"> ➤ To reduce reimbursement payments ➤ To benefit those requiring multiple drugs ➤ To increase government revenues ➤ To reduce pharmaceutical spending

¹Pharmaceuticals Pricing Board, ²Value Added Tax, ³Voluntary generic substitution became operational in 1993

In April 2009, generic substitution was complemented by the reference price system (278). At the same time, generic substitution was extended to cover drugs with holding an analogous process patent. Under the reference price system, certain medications containing the same active substance in an equal composition and being sold in comparable package sizes are allocated to the same reference price group. Thus, each medication in the same group carries the same price regardless of its market price. The reference price groups are based on the list for substitutable medicinal products approved by the FIMEA, and the reference prices are determined on a quarterly basis by the PPB. A reference price is calculated within the group from the most inexpensive product by adding 1.50 € if the price is less than 40.00 € and by adding 2.00 € if the price is 40.00 €

or more. Reimbursements for medications covered by the system are paid on the basis of the reference price rather than the retail price. Customers who refuse to switch to a cheaper drug are reimbursed according to the reference price and will have to pay the difference themselves. Only the doctor may prohibit substitution by making a note of this on the prescription (278).

The first year of reference pricing and extended generic substitution generated total cost savings of 110 million € (278). The savings were the greatest in antipsychotics (27 million €), lipid-modifying agents (19 million €) and agents acting on the RAAS (13 million €). These drugs also generated the greatest savings in reimbursement costs. About 90% of the savings were attributable to generic substitution being extended to cover drugs holding an analogous process patent; about three-quarter of these savings arose from atorvastatin (i.e. lipid-modifying agent) and losartan (i.e. ARB) as well as quetiapine and olanzapine (i.e. antipsychotics). Until the end of 2009, about half of all reimbursable medicinal products with marketing authorization were included in the reference price system (278).

Biosimilar medicines have since 2006 been accepted to the EU markets. Biosimilars are follow-on versions of original (“reference”) biological medicines (such as growth hormones or erythropoietins) (289). They are not identical to generics due to their complex nature and production methods. Biosimilars are independently developed after the patent of the original product has expired but are less expensive than the original products (289).

2.4.7 Pharmaceutical patents

Although these legislative measures led to substantial temporal savings both in the sales of medicines and in the reimbursed expenditure, the costs of medications continue to increase because new drugs are more expensive than old ones, at least as long as they are protected by their patents. In terms of sales, the largest medication groups in 2012 were the antineoplastic and immune-modulating agents, as well as the drugs affecting the alimentary tract and metabolism (279). In fact, in recent years many new drugs belonging to these groups, such as drugs for cancer, rheumatoid arthritis and diabetes, have been developed and have reached the market. To recoup the costs of research and drug development, the manufacturers may charge a relatively high price for a new patented drug. Because only minimal numbers of pharmaceutical agents developed enter the market, the successful drug development process must also cover the development costs of unsuccessful drugs. Moreover, pharmaceutical companies also make substantial investments in the marketing of the new drugs to physicians and pharmacies (290).

The life cycle of a drug can be divided into three phases: 1) research and development of a drug until the drug obtains a marketing authorization, 2) the period during which the pharmaceutical company has the exclusive right to sell the drug and 3) the period after the patent expires, allowing generic or biosimilar competition (291). To assure the safety, efficacy and availability of a new drug, the pharmaceutical industry is heavily regulated by the Government, covering the entire life cycle of a medication.

A pharmaceutical patent provides the manufacturer with an exclusive right to sell the new medicine for up to 20 years from the date of the patent filing (Patents Act, 550/1967, section 40, subsection 1). In practice, drug development is an expensive, time-consuming and uncertain process that takes years to complete. On average, it takes 10–12 years and costs about \$1 billion to discover and develop a new drug (Pharma Industry Finland, <http://www.pif.fi/en>). Therefore, by the time a new drug has been launched to the market and been granted a reimbursement status, the manufacturers may have less than 10 years left of the patent exclusivity.

Until 1995, patents could not be granted for medicinal products in Finland; only an analogous process patent protecting the production method was available. Only after 1995 was a product patent provided by the Finnish legislation. Moreover, before 2005 the data exclusivity period in Finland for new drugs, which was the only way to restrict the introduction of generic products, was only six years. From the viewpoint of manufacturing companies, weaker analogy process patents and a relatively short data exclusivity period have contributed to a development where marketing authorizations for generic products have often first been applied in Finland. Until 2006, generic substitution was applied also to products with valid analogy process patents, but thereafter they were excluded (Government Proposal 108/2005). In 2009, drugs with an analogous process patent became substitutable within the generic substitution regime and were subjected to price competition again (278).

To compensate for the long development times of drugs and the relatively short effective patent times, pharmaceutical companies have since 1993 been able to obtain a supplementary protection certificate to extend the duration of the exclusive right up to a maximum of five years [Regulation (EC) 469/2009]. After harmonization at the European Union level in 2005, pharmaceutical companies may enjoy eight years of data exclusivity (i.e. their pre-clinical and clinical trial data may not be referenced in the regulatory filing of another, typically generic, company for the same drug substance) with an additional two-year term of marketing exclusivity (i.e. after a period of 10 years from granting of the marketing authorization to the innovator company, the generic company can also market their product) and a potential one-year extension for new therapeutic indications (Directive 2004/27/EC).

However, during the market exclusivity period a new patented drug may face competition from other products for the same disease or products having a near-comparable effect or chemical structure as the original medicinal product with only minor differences (so-called me-too drugs) (292). Moreover, parallel imported medicinal products may create price competition. In the European Union, based on the principle of free movement of goods (Treaty on the Functioning of the European Union, Article 34–36), other (parallel importer) than the holder of the marketing authorization can buy the patented medications from countries where the drugs are cheaper (e.g. Mediterranean countries) and import them to the more expensive ones (e.g. Germany and Scandinavian countries), thus obtaining lucrative margins (293). In Finland, the first marketing authorizations for parallel import products were granted in 1996, but parallel import has generated only marginal savings. The proportion of parallel import products is only 1–2% of the Finnish pharmaceutical markets (290). Also, pharmaceutical companies have adopted several strategies to extend the period of the market exclusivity of their drugs

(294). They may obtain additional patents by developing new formulations (only minor differences from the original drug) that promote patient compliance through reduced dosing or side-effect profile, or by developing new routes of administration or new indications of drugs.

2.5 Diabetes guidelines

Type 1 diabetes is a challenging and complex disease to be managed successfully, with the major responsibility for the day-to-day care resting with the patients and their families. Over the past decades, numerous diabetes guidelines have been developed to assist clinicians and other health care workers in making evidence-based management decisions. This, in turn, may lead to better diabetes care outcomes by bringing the best knowledge to daily care, minimizing unnecessary variation of care and optimizing the effectiveness of care (295, 296). There are several existing international and national diabetes guidelines, as well as guidelines generated by joint interests [e.g. European Society of Cardiology and European Association for the Study of Diabetes (ESC/EASD) guidelines for the management of diabetes and CVD] (297).

2.5.1 American Diabetes Association (ADA) Guidelines

The ADA has been actively involved in the development of diabetes care standards and guidelines (7). The ADA guidelines are one of the leading diabetes guidelines; the ADA recommendations have strongly influenced other diabetes guidelines (298). The ADA provides, on an annual basis, recommendations on the screening, diagnostic and therapeutic actions applicable to most people with diabetes (7). These recommendations are regularly updated based on new evidence, or in some cases, to clarify earlier recommendations, by the ADA's multidisciplinary Professional Practice Committee. The guidelines are evidence-based wherever possible, but may also have been drawn from accumulated professional knowledge and consensus agreement. Therefore, the ADA has adopted a quality grading system showing the level of evidence that supports each recommendation. A-level evidence is based on large well-designed clinical trials or well-conducted meta-analyses, B level is supportive evidence from well-conducted cohort studies or a case-control study, and C level is supportive evidence from poorly controlled or uncontrolled studies. "E" refers to an expert consensus or the recommendation being based on clinical experience (7).

2.5.2 Glycaemic, BP and lipid control

The ADA guidelines include targets and strategies for glycaemic, BP and lipid control applicable to most adults with diabetes. Over the years, these targets have been revised based on new evidence. For decades, in response to the DCCT and the United Kingdom

Prospective Diabetes Study (UKPDS) data, the ADA has recommended maintaining HbA_{1C} levels below 7% in adults with diabetes (299). The treatment target for LDL-C has become more stringent with time, especially in those with known CVD (300). However, the cut-off value for systolic BP has been under constant debate. Recently, the treatment target for systolic BP has been revised from less than 130 mmHg to less than 140 mmHg. The previous systolic BP target had been derived from observational studies rather than randomized controlled clinical trials (141). Randomized clinical trials (where all patients had type 2 diabetes) demonstrated the benefit of lowering systolic BP to below 140 mmHg, but the evidence is limited (301, 302).

Recent ADA guidelines emphasize a more individualized approach in the management of diabetes by taking into account the patient's individual preferences, co-morbidities and other patient-specific factors when deciding the patient's treatment goals and strategies (7). Consequently, based on a benefit-risk assessment, the more stringent targets for HbA_{1C} (i.e. 6.0–6.5%) may be reasonable for younger, healthier patients with a short duration of diabetes, a long life expectancy and no CVD if they can be achieved without excessive hypoglycaemia. In contrast, the less stringent HbA_{1C} targets (i.e. 7.5–8.0%) may be better suited for older and more frail patients with multiple co-morbidities, a long duration of diabetes and a history of severe hypoglycaemia (7, 303). Also a lower systolic BP target, e.g. less than 130 mmHg, may be appropriate for younger patients with a long life expectancy or for those who carry a high risk of stroke if it can be achieved with fewer drugs and without significant adverse effects (141).

2.5.3 Achievement of treatment targets

Despite strong evidence that intensified glycaemic, BP and lipid control reduces the risk of microvascular complications and cardiovascular disease and improves the prognosis of patients with DN, implementation of the evidence-based treatment targets is challenging in clinical practice. **Table 4** summarizes the studies during the last two decades that have reported the achievement of HbA_{1C}, BP and LDL-C targets either simultaneously in patients with diabetes or the achievement of each target separately in patients with type 1 diabetes.

Cut-off values of treatment targets, data collection time and study population differ in these studies. Moreover, the majority of the patients had type 2 diabetes, and very few of the studies reported the achievement of the three target values in the same individual simultaneously in patients with type 1 diabetes. In general, these studies show conspicuous discrepancies between evidence-based treatment targets and actual clinical results since only a minority of the patients had reached the targets proposed by the ADA. This suggests that some patients may have a suboptimal medication regimen (i.e. insufficient daily doses or numbers of the drugs) or poor adherence to the treatment and lifestyle changes. Especially patients with hypertension might require multiple drug therapy to reach treatment targets (201). However, certain subgroups of the patients with diabetes are considered to have treatment-resistant hypertension (RH). RH is defined as failure to achieve the target BP even after using a minimum of three antihypertensive drugs at maximally tolerated doses, from different classes, one of which should be a

Table 4. Achievement of HbA_{1C}, blood pressure and LDL cholesterol targets among adult patients with diabetes.

	Cohort	Data collection time and treatment targets	Results
Ali et al., 2013, USA (NHANES ¹) (12)	10 665; Diabetes; National population-based	1999–2010 HbA _{1C} < 7% BP < 130/80 mmHg LDL-C < 2.6 mmol/L All three targets achieved + non-smoking status	1999–2000 44% 2003–06 57% 2007–2010 52% 40% 45% 51% 36% 47% 57% 5% 10% 14%
Cheung et al., 2009, USA (NHANES) (304)	17 306; Diabetes; National population-based	1999–2006 HbA _{1C} < 7% BP < 130/80 mmHg LDL-C < 2.6 mmol/L All three targets achieved	1999–2002 43% 2003–2006 57% 39% 45% 36% 47% 7% 12%
Braga et al., 2012, Canada (305)	3002; Type 2 diabetes; Primary care settings	2005–2006 HbA _{1C} ≤ 7% BP ≤ 130/80 mmHg LDL-C < 2.5 mmol/L All three targets achieved	39% 30% 53% 7%
Beaton et al., 2004, New Mexico, USA (306)	7114; Diabetes; Managed care organisation	1999–2000 HbA _{1C} < 7% Systolic BP < 130 mmHg Diastolic BP < 80 mmHg LDL-C < 2.6 mmol/L	37% 41% 54% 23%
Valle, 2010, Finland (307)	967; Type 1 diabetes; Finnish cohort	2009–2010 HbA _{1C} < 7.5%* BP < 130/80 mmHg BP < 135/85 mmHg* LDL-C ≤ 2.5 mmol/L All three targets achieved (* + LDL-C < 2.6 mmol/L)	22% 28% 39% 58% 7%
Livingstone et al., 2012, Scotland, UK (308)	9276; Type 1 diabetes; Scottish diabetes register	2008 HbA _{1C} < 7% BP < 130/80 mmHg	13% men 30%; women 47%
Bryant et al., 2006, Sydney, Australia (10)	96; Type 1 diabetes; Sydney teaching hospital	2003 HbA _{1C} < 7% BP ≤ 130/80 LDL-C < 2.6 mmol/L	13% treated 29%, untreated 60% treated 60%, untreated 36%

¹National Health and Nutrition Examination Survey

diuretic (309, 310). Also patients with controlled BP who are taking four or more antihypertensive drugs may be considered resistant to treatment (310).

2.5.4 Adherence to medication

Poor adherence to medication regimens has frequently been reported in patients with chronic conditions, including diabetes, hypertension and cardiovascular disease (311). Adherence to a medication regimen is defined as patients taking their medication as prescribed by their physician and continuing to take a prescribed medication (312, 313). The WHO estimates that adherence to long-term therapies for chronic illness is as low as 50% in the developed world (314). In a prospective study, 40% of patients with newly

diagnosed hypertension discontinued their antihypertensive medication during the first year of treatment (315). Poor adherence may, however, be less common in patients with diabetes. A recent study reported that only 20% of family practice patients with type 2 diabetes and hypertension showed poor adherence to their antihypertensive treatment (316). In general, better adherence rates for medication use than for diet and physical activity were reported in patients with diabetes (317-319). According to the Cross-National Diabetes Attitudes, Wishes and Needs (DAWN) Study, self-reported adherence to medication was 83%, to diet 39% and to exercise 37% in patients with type 1 diabetes (317).

A systematic review, including 17 studies, showed that self-reported rates of adherence to insulin therapy in patients with diabetes ranged from 43% to 86% (320). As expected, higher adherence rates for insulin therapy have been reported by patients with type 1 diabetes than by patients with type 2 diabetes. This is certainly related to the more vital role of insulin therapy for glycaemic control and the higher risk of life-threatening events as a result of total insulin deficiency in the patients with type 1 diabetes. A small study showed that among young people with type 1 diabetes 28% of the patients obtained less insulin than their prescribed dose (321). Notably, adolescents (10–19 years) had the poorest adherence to insulin as compared with those younger than 10 years or those 20–30 years old. That study also reported that lower adherence was associated with more hospital admissions for acute diabetes complications and diabetic ketoacidosis.

The consequences of medication non-adherence are not only related to poor clinical outcomes but also to an increase in unnecessary health care costs (322-324). To improve a patient's adherence to a long-term medication regimen, it is important to recognize and understand the factors that challenge medication adherence. The reasons for poor adherence are often multifactorial, including patient-related factors (such as age, education, depression, health literacy, substance abuse), environmental factors (such as social network and support), health care provider factors (such as communication, relationship with patients), health care system factors (such as access to care, transitions of care, out-of-pocket costs of medication, health insurance) and disease- (symptoms, duration, response to treatment) and treatment-related factors (adverse events, polypharmacy, regimen complexity) (177, 311, 312, 324).

Lower adherence to medication has frequently been shown when the condition is chronic and when the course of symptoms varies or the symptoms are not apparent and do not physically hurt or the treatment is aimed at asymptomatic conditions to prevent adverse events years later (312, 325-327). Therefore, adherence to the regimen may be jeopardized when ACE inhibitor or ARB treatment has been prescribed for microalbuminuric normotensive patients, when lipid-lowering therapy is initiated for patients at CVD risk or when combinations of antihypertensive drugs are required to reach BP targets.

Moreover, the complexity of the regimen, including numerous medications (polypharmacy) and multiple dosing schedules, may be related to non-adherence (328). Previous studies have shown that the percentage of adherence is inversely correlated with the number of drugs and the frequency of doses (327). A recent study from managed care settings assessed the effect of the previous prescription burden on future adherence when antihypertensive and lipid-lowering therapy was added (329). The adherence rates during

the first year after therapy initiation decreased to 41%, 35% and 30% in patients who were taking none, one and two prescription medications, respectively, prior to starting the antihypertensive and lipid-lowering medication. In a meta-analysis, the adherence rate decreased significantly with increasing frequency of dosing; adherence to once-daily dosing was 79%, twice-daily dosing 69%, 3 times per day dosing 65% and 4 times per day dosing 51%. Another meta-analysis from 42 trials showed that using a fixed-dose combination of antihypertensive therapies was associated with higher compliance and less hospitalizations than the use of separate pills (330). Several strategies to improve dosing schedules exist, including the use of pill boxes to organize daily doses, new technologies such as reminders by personal digital assistants and simplifying the regimen to daily dosing or prescribing fixed-dose combination therapies (312, 330).

Finally, experience or fear of adverse effects is one of the most common barriers to medication adherence (327). In the DCCT study, patients receiving intensive therapy were two to three times more likely to experience a severe hypoglycaemic episode than those receiving conventional therapy (183). Thus, fear of hypoglycaemia is likely to be an important barrier to achieving blood glucose targets (331). Importantly, fear of hypoglycaemia may lead to a tendency to accept and maintain hyperglycaemia, and this, in turn, may lead later to diabetic complications (332). Patients with type 1 diabetes make regular visits to the outpatient clinic or they see their general practitioner at 3- to 6-month intervals. Adverse effect profiles should be considered not only when prescribing a new drug, but also at every visit thereafter (312).

The review of the literature above revealed several factors that may have direct or indirect effects on medication use and cost in patients with type 1 diabetes. *Figure 2* summarizes the main factors.

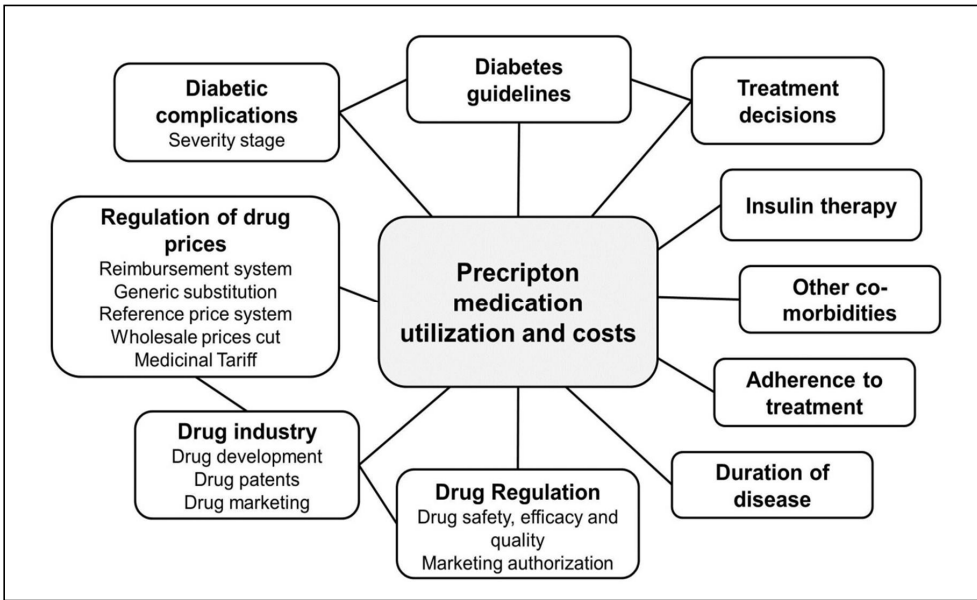


Figure 2. Factors affecting prescription medication use and cost in patients with type 1 diabetes.

2.6 Economics of diabetes

This section explores the economic burden of diabetes. First, a brief overview of cost-of-illness (COI) analysis is provided. This is followed by descriptions of the direct and productivity (previously called indirect) cost of diabetes as well as the economic burden of DN. Finally, findings related to the use and costs of medication, especially in outpatients with type 1 diabetes, are presented.

As health care resources are limited, their efficient use is crucial. To optimize the use of health care resources and to determine the cost-saving strategies for the management of patients with diabetes, policy-makers should be familiar with the cost structure of diabetes care as a whole and at various stages of the disease process, including the effects of the most prevalent diabetes-related complications. Basically, two main approaches to evaluate economic aspects of care exist: economic evaluation and COI analysis. The basic tasks of economic evaluation are to identify, measure, value and compare the costs and consequences of alternative courses of action (333). COI is a descriptive study design that identifies and measures a particular disease's total costs to society, including direct, productivity and intangible dimensions (334). It can also provide information about the main cost components and their proportion of the total costs, the cost variability and the distribution of costs in the course of disease progression (335). COI can also consider preventive measures by providing estimates of the savings that potentially accrue through successful prevention, e.g. the amount that could be saved if a disease were to be eradicated (335).

2.6.1 Cost-of-illness analysis

In the COI analysis, the direct medical costs include expenditures for hospitalization, outpatient care, nursing home care, services of physicians and other health care specialists, rehabilitation, special devices needed, diagnostic tests and medication. Non-medical costs are transportation costs, relocation expenses and informal care. Productivity costs represent productivity losses related to morbidity and mortality. Intangible costs refer to the patient's psychological pain, discomfort, anxiety and distress related to the disease, and they are usually measured in forms of quality of life. (334, 335)

Moreover, the COI analysis can be described according to the perspective, approach and methods chosen. The research question guides the most appropriate perspective. The perspective could be that of the patients (e.g. out-of-pocket costs), the employers (e.g. cost of worker's compensated insurance premiums and loss of productivity), the insurance company (e.g. cost of claims), the government (e.g. cost of public health services) or the society, which is the most comprehensive and commonly used perspective in COI studies (336).

COI analysis can be either prevalence- or incidence-based. The prevalence-based approach refers to the total number of cases within a specified time period (typically one year), while the incidence-based approach refers to the new number of cases arising in a predefined period of time (335). Thus, a prevalence-based study involves estimates of the costs occurring in the given term and an incidence-based study calculates the value of

lifetime costs for new cases of disease. In the prevalence-based approach, COI studies may yield useful information to decision-makers by drawing their attention to conditions where the burden has been underestimated or by providing a picture of the major cost components, and thus, the areas where the cost containment policies would have the greatest impact (336). The incidence-based approach is especially useful when estimating the savings of the preventive measures, when analysing the management of the disease from onset until death or when showing how the costs are distributed during illness progression. This could encourage the development of clinical practice guidelines aimed at increasing effectiveness and efficiency of disease management (335).

Finally, two basic methods exist for quantifying the resources: top-down (“population-based”) and bottom-up (“person-based”) methods (337). The top-down approach is based on aggregate data (available from national health care statistics or registers) on mortality, morbidity, hospital admissions, general practice consultations, disease-related costs and other health-related indicators. Costs are calculated by multiplying the total health care expenditures by the proportion of health care services used by the disease group. In the bottom-up approach, the resources used are calculated from individuals with the health problem in question; the average cost of treatment (sum of all components of treatment) is multiplied by the prevalence of the health problem in question (338). The average per-person costs may be extrapolated to the whole population using relevant epidemiological data. The bottom-up approach is a more comprehensive one, allowing identification of differences in demographic and clinical characteristics between patients (337).

By estimating the resources used and lost as a result of a particular disease, COI studies provide an important economic guide for policy development, priority settings and management of disease (339). Thus, COI studies may provide a framework for cost estimation, and hence, may direct health economic research towards cost-effective methods for diabetes care. The chronic nature of diabetes and its association with many complications lead to a considerable economic burden on society. The next section provides information about the economic costs of diabetes. The section also illustrates the major cost drivers as well as the effects of the complications on costs.

2.6.2 Costs of diabetes

As the number of people with diabetes grows worldwide, the disease imposes an increasing economic burden on national health care budgets. Globally, approximately 11% of the annual health care expenditures were spent on diabetes in 2013 (3). However, there is a substantial disparity between countries; only 20% of the global health expenditure comes from low- and middle-income countries, where about 80% of the people with diabetes reside (3). While the US alone constituted about 36% of the global expenditure on diabetes, China, the country with the largest population with diabetes, comprised only 7% of the world total. Also in Finland and several other European countries, the annual health care costs for diabetes represent more than 10% of the health care expenditure, and these costs are to a large extent due to the escalating costs of complications (13, 14). A recent Finnish study estimated that the health care costs of diabetes together with the lost

labour inputs of afflicted patients will reduce the Finnish gross domestic product (GDP) by over 1% in the long run (340).

Over the last few years, several economic studies of diabetes from different countries and continents have been published. In general, these studies have confirmed that diabetes causes a significant burden not only to the health care system but also to individuals and society as a whole. It is challenging, however, to compare the total costs of diabetes between different countries because different studies vary markedly in study designs, settings, populations, data sources, study periods and publication years. Moreover, methodological differences and inclusion of different cost components exist. Also, the accuracy of the data sources used may vary considerably. Typically, a clear distinction between the various types of diabetes has not been made, or the majority of patients have had type 2 diabetes. In addition, the costs have rarely been calculated separately for the different diabetic complications or severity stages of disease.

A systematic review (336), in which a total of 30 COI studies of diabetes (published between 2007 and 2011) were included, highlighted the variability of the studies. The annual direct costs of diabetes ranged from US\$146.1 million in Iran to US\$174 billion in the US, and the annual direct cost per patient from US\$150 in India to US\$14 060 in the US. The authors of the review highlighted two main findings. Hospitalization seemed to be the major direct cost driver. Moreover, the lack of standardized COI methods, and variability in study designs, perspectives and included cost categories made direct comparisons virtually impossible.

The ADA has regularly reported the economic cost of diabetes in the US. They have built the Cost of Diabetes Model by combining information from the peer-reviewed literature, government statistics, original analyses and medical claims databases. A prevalence-based approach was used to estimate the medical costs by demographic group, health service categories, and medical conditions. The number of people with diagnosed diabetes continues to rise. While in 2002, about 12.1 million people had been diagnosed with diabetes in the US (341), this figure had increased to 17.5 million in 2007 (9). However, the latest updated report (342) estimated that nearly 22.3 million people (about 7% of the US population) had been diagnosed with diabetes in 2012. At the same year, the total estimated cost of diabetes reached \$245 billion, including \$176 billion for direct costs and \$69 billion for productivity loss incurred. The total costs had increased more than 40% from the year 2007.

The largest components of the medical expenditures were hospital inpatient care (43%), followed by prescription medication to treat diabetic complications (18%), antidiabetic agents and diabetes supplies (12%), physician office visits (9%) and nursing/residential facility stays (8%). Notably, prescription medications, insulins, and other antidiabetic agents represent over one-quarter (28%) of all health expenditures attributed to diabetes. The health care expenditure per patient was \$13 700 per year; it was about two to three times higher than the expenditure would have been without diabetes. Notably, about 59% of the direct medical cost was derived from the population aged 65 or more, and about 88% of the indirect cost was attributed to the population under 65 years of age. A distinction between the various diabetes types was not made in that study, and hence, type 1 diabetes was not a specific research priority.

Despite the challenge of distinguishing the cost of different diabetes types from medical claims, Dall et al. (343) estimated the cost by diabetes types in 2007 based on the same Cost of Diabetes Model built by the ADA (9). Moreover, medical claims were analysed to estimate the proportion of diagnosed diabetes cases (according to the criteria characteristic to each diabetes type used in previous studies) and excess medical costs by diabetes type. The authors estimated that about 5.7% (~1.0 million) of the 17.5 million people with diagnosed diabetes had type 1 diabetes. About \$19.4 billion of the total costs were associated with type 1 diabetes (8.6%). Medical costs accounted for \$10.5 billion and indirect costs for \$4.4 billion. Costs associated with type 2 diabetes were \$159.5 billion (including medical costs of \$105.7 and indirect costs \$53.8). Although the costs associated with type 2 diabetes were significantly higher, the economic burden per case of diabetes was greater in type 1 diabetes than in type 2 diabetes, and the difference increased with age. While the total cost per case of type 2 diabetes was \$9200 to \$9700 across all age groups, the cost was \$4044 for people with type 1 diabetes who were younger than 44 years and \$35 365 for those aged 65 or older. That increase was mainly due to higher utilization of institutionalized care in the older age group. However, the results of that study should be treated with some caution. The cost analysis was largely based on claims data, which tends to be less accurate than medical records when identifying patients with a special condition (e.g. diabetes type).

The economic burden of diabetes was estimated by Jarvala et al. (13) in Finland in 2007. The data of the inpatient care, outpatient visits in specialized care, prescription medication and productivity loss (workday absence due to sickness, premature retirement, premature mortality) were collected from the national registers between 1998 and 2007. Moreover, outpatient visits in primary care were estimated from the Health 2000 survey. In that prevalence-based COI study, the costs were assessed from a societal perspective. The number of patients with diagnosed diabetes was 284 832, and of these 39 575 (14%) had type 1 diabetes in 2007. In the same year, the estimated total medical cost of diabetes was 1.3 billion €, the majority of which was the incremental cost of diabetes (830 million €). The incremental cost of diabetes was calculated by using the average medical costs of the population (the average medical costs of the people with diabetes – the average medical costs of the population). The cost of productivity loss was also 1.3 billion € in 2007.

In patients with type 1 diabetes who had at least one complication, medical costs were on average 2.4 times higher, and in patients with type 2 diabetes and one complication 3.2 times higher than the cost of diabetes in patients without any complications. The largest component of medical costs was specialized inpatient care (26%), followed by medication (25%) and primary inpatient care (18%). The total medication costs were about 324.8 million € in 2007, and these costs increased by approximately 7.9% per year between 1998 and 2007 (adjusted to 2007 euro levels by using the Consumer Price Index). In patients with type 2 diabetes, the total medication costs were 263 million € and the costs per patient 1040 € in 2007. The corresponding numbers in patients with type 1 diabetes were 61.7 million € and 1450 €.

In a case-controlled, prevalence-based study, Kangas (20) estimated the use of health care services as well as total and incremental direct costs of health care in individuals with diabetes in Helsinki, Finland in 1997. Data of the consumption and direct costs of care

services were obtained from different registers, including outpatient and inpatient services, medications, self-care equipment and travel costs. Dental, psychological and occupational health services were not included. Outpatient and inpatient costs were studied on the basis of average prices and actual expenditures. The national estimate for the total costs of services of the population was also assessed by extrapolating the results from Helsinki to the national level. The costs of care for people with type 2 diabetes were two times higher and for patients with type 1 diabetes four times higher than for those without diabetes. For both types of diabetes, about one-third of the patients had at least one complication and these patients accounted for two-thirds of the total treatment costs. Complications brought a 10-fold increase in medical costs of care for people with type 1 diabetes and a 20-fold increase for people with type 2 diabetes. The costs of medication were about 16% of the total costs, and diabetes drugs accounted for one-third of these costs.

It is complicated to compare these two Finnish studies due to methodological differences. While Kangas (20) estimated the incremental costs of diabetes by using age- and gender-matched controls without diabetes, Jarvala et al. (13) calculated the incremental costs of diabetes by using the average medical cost of the Finnish population. The former method may give a more precise figure of the incremental costs. The study was conducted in one city only, and the results were then extrapolated to the national level. However, Jarvala et al. estimated the costs by using for the most part nationwide register data, which may give a more relevant and comprehensive picture, even if the risk of misclassification may increase in register-based studies. The Kangas study is over 15 years old, and many factors related to management of diabetes have since changed. Thus, the cost estimates are unlikely to be accurate estimates of the current costs of diabetes. Nevertheless, the older study showed how important is to differentiate the costs between the two diabetes types, as proportion, age and gender of patients as well as the treatment and related problems may vary between type 1 and type 2 diabetes.

2.6.3 Economic burden of diabetic nephropathy

Only a few studies have been conducted that have estimated the economic burden of DN. In these studies, the majority of the patients have had type 2 diabetes. These studies have different study designs, perspectives and cost components. Also the accuracy of data sources has varied between the studies. None of the studies was conducted in Finland. Nonetheless, this section illustrates the economic burden associated with the progression of DN.

Gordois et al. (88) quantified and compared the rates and annual direct costs of DN (including patients with microalbuminuria, overt nephropathy and ESRD). The COI model was constructed to estimate the annual costs. In the US the costs were estimated from the perspective of the health care payer and in the UK from the perspective of the National Health Service. In the US, the estimated number of patients with diagnosed diabetes was 11.1 million, 0.83 million of whom had type 1 diabetes, while the corresponding figures in the UK were 1.4 million and 0.17 million. The total annual costs of DN were estimated to be \$16.8 billion in the US and \$1.2 billion in the UK. For type 1 diabetes, the estimated costs were \$1.9 billion in the US and \$231 million in the UK. In the US for every 10%

increase in the prevalence of microalbuminuria the total annual costs increased by 2%. Moreover, every 10% increase in the prevalence of overt nephropathy increased the costs by 5.5% in the US and by some 7% in the UK. In both countries, people with type 1 diabetes incurred a relatively large amount of the total cost of DN. In the US, the proportion of patients with type 1 diabetes was 7.5%, but they accounted for 9% of the total costs of DN. Similarly, in the UK the proportion of type 1 diabetes patients was about 12%, but they accounted for 20% of the total costs of DN. These figures could be explained by the larger number of patients with ESRD and a new kidney transplant in the patients with type 1 diabetes. Importantly, the evaluation was conducted already 13 years ago. Moreover, some inaccuracy of the estimates may have led to underestimation or overestimation of the total costs. Despite these shortcomings, the study confirmed the enormous economic burden of DN on the health care system.

Nichols et al. (344) estimated the direct medical costs of 7758 hypertensive patients with type 2 diabetes according to the level of proteinuria. They also compared the costs between the patients whose DN did and did not progress. The data were obtained from the Kaiser Permanente North-West diabetes registry and the patients were followed for up to eight years for progression of DN. At baseline, 67% of the patients were normoalbuminuric, 28% microalbuminuric and 5% macroalbuminuric. Unadjusted mean annual costs at baseline were \$6455 for those with normoalbuminuria, \$7398 for those with microalbuminuria and \$8087 for those with macroalbuminuria. The mean pharmacy costs did not differ significantly between those with normo- and microalbuminuria (\$2333 vs. \$2510). However, these costs were higher in individuals with macroalbuminuria (\$2781, $P < 0.001$) than in those with normoalbuminuria. About half of the patients with normoalbuminuria progressed to a higher stage, and about one-third of the patients with microalbuminuria progressed to macroalbuminuria during the follow-up. Only 5% of the patients with macroalbuminuria progressed to ESRD. The authors reported that the mean costs increased by 37% following progression from normo- to microalbuminuria (\$7424 vs. \$10 188); and 41% following progression from micro- to macroalbuminuria (\$8753 vs. \$12 371), after adjustment for demographic and clinical characteristics. That study showed that the progression to a more severe stage of DN was strongly associated with higher medical costs. However, all patients were diagnosed with type 2 diabetes.

In a retrospective German study (345), 118 diabetes patients' direct and indirect costs related to DN were estimated in 2002. Costs per patient were calculated from the societal and health insurance perspective according to the three stages of DN: microalbuminuria, macroalbuminuria and renal insufficiency. From the societal perspective, the costs per patient related to DN were 2019 € and from the health insurance perspective 1332 €. From the societal perspective, the costs were similar between micro- and macroalbuminuric patients (685 €), but were considerably higher in patients with renal failure (10 223 €). The corresponding numbers from the health insurance perspective were 222 €, 398 € and 7862 €. The main cost drivers were dialysis (38%), retirement (19%) and medication (14%). In this study, only DN-related costs were estimated, and therefore, these results are more likely to underestimate the real costs. DN is often associated with other adverse conditions, such as hypertension, neuropathy, retinopathy, hypercholesterolaemia, hyperlipidaemia and coronary heart disease. In fact, it is impossible to restrict the costs only to those due to nephropathy only. Moreover, classification between the types of

diabetes was not done and also the number of cases was low. The authors assumed that the annual resource use with respect to stage of DN is equal in patients with type 1 and type 2 diabetes.

2.6.4 Use and costs of medication

Prescription medications represent the second largest proportion of the total costs of type 1 diabetes (20, 346). In Finland, the costs of prescription medications accounted for approximately one-third of the total costs of type 1 diabetes (20). Insulin therapy is one of the main elements of the direct costs of type 1 diabetes. Often, individuals with diabetes also have a high overall usage of medications, independent of the treatment needed for diabetes itself.

There are several studies concerning medication use and costs of diabetes. These studies have focused on medication use and cost solely (16-19) or the drug costs have been evaluated as part of the total medical costs in patients with diabetes (58, 346-348). Moreover, some of the studies have focused on diabetes medications only (349, 350).

The following section illustrates some general trends in the use and costs of prescription medications in patients with diabetes. The first three studies are cross-sectional and the other two show longitudinal trends. In order to focus on the use and costs of prescription medications in patients with type 1 diabetes, only such cross-sectional studies where patients have been stratified according to diabetes types (type 1 and type 2) were included. **Table 5** summarizes the results of different studies concerning the costs of prescription medications in patients with diabetes and their controls. The table also shows costs of diabetes drugs.

In a population-based study, Bruno et al. (16) compared prescription drug use and costs in patients with diabetes (n= 33 797) and non-diabetic individuals (n= 863 879) in a large population-based cohort in the city of Turin, Italy. About 5% (n=1704) of the patients had type 1 diabetes. The data were obtained from the Piedmont Diabetes Registry, hospital discharges and prescription data sources. All prescriptions registered over a 12-month period in 2003–2004 were examined. The overall mean prescription cost per year was 831 € in patients with diabetes and 183 € in non-diabetic individuals. Estimates derived from the age- and sex-adjusted model showed almost threefold higher mean costs in patients with diabetes than in non-diabetic individuals. Notably, the mean costs were almost eight times higher in patients with type 1 diabetes than in controls. Glucose-lowering drugs accounted for almost 19% of the total costs (45% in type 1 and 17% in type 2 diabetes). Cardiovascular drugs were three times more often prescribed to those with diabetes than to non-diabetic individuals. One-third of the diabetic patients received anti-thrombotic treatment, mainly aspirin (19% of type 1 and 33% of type 2 diabetes). Of the patients, 28% used lipid-lowering drugs (17% of type 1 and 29% of type 2 diabetes). Only one-third of the patients were prescribed drugs for the prevention of CVD and chronic kidney disease such as ACE inhibitors, statins and aspirin. The authors estimated that from the public health perspective the costs of medication would increase in the future if the evidence-based diabetes guidelines were implemented in clinical practice more effectively.

Reunanen et al. (17) estimated the overall use and costs of medications and co-morbidity of drug-treated diabetes patients, compared with sex- and age-matched control subjects in Finland. The data were obtained from the national drug registers. From the registers, 16 955 type 1 diabetes and 68 717 type 2 diabetes patients were identified in 1995. The use of almost all kinds of medication was greater in diabetes patients than in controls. The mean costs of medications for individuals with type 1 diabetes were 12 times greater than the costs of medications taken by control subjects. Insulin treatment accounted for 62% of the costs, but even after excluding the costs of insulin, the mean costs were still over five times greater than the costs of medications for control subjects. Regarding the patients with type 2 diabetes, the mean costs were three times greater than in controls, and when the diabetes drugs were excluded the costs were two times higher. Type 1 diabetes patients used all types of cardiovascular medications more often than controls. This study was, however, cross-sectional concerning the drug costs and the co-morbidities in one year, 1995, with varying duration of diabetes. The study was conducted almost 20 years ago, and meanwhile, the management of diabetes has changed and many new drugs have reached the markets. Therefore, these results may not reflect current medication use and costs in patients with diabetes in Finland.

Evans et al. (19) described the prescribing rates of drugs in patients with diabetes and non-diabetic individuals in Tayside, Scotland, in 1995. A population-based diabetes register was used to identify patients with type 1 and type 2 diabetes. A computer algorithm was used to identify patients with type 1 diabetes. Patients who were diagnosed when younger than 35 years of age and with a requirement for insulin were categorized as type 1 diabetes patients. There were 406 526 patients in Tayside, and of these 7843 had diabetes (974 type 1 and 6869 type 2 diabetes). A database of all prescriptions dispensed in the community was used to investigate the drug utilization. Drugs were categorized according to four drug categories: gastrointestinal, cardiovascular, central nervous system and infections.

The mean dispensed prescribing rates for all drugs (diabetes medications excluded) were higher across all age groups for patients with diabetes than for individuals without diabetes. After adjusting for age, the patients with type 1 diabetes were 2.07 times more likely and the patients with type 2 diabetes were 1.70 more likely to be dispensed a drug item than people without diabetes. Patients with diabetes accounted for 7.3% of the prescriptions dispensed (0.7% of the patients with type 1 diabetes and 6.6% of the patients with type 2 diabetes). The research group highlighted the higher usage of all prescription drugs in patients with diabetes. However, type 2 diabetes constituted a particular burden because there were 8 times more of them, and they used more drugs than type 1 diabetes patients.

Rathmann et al. (18) illustrated how outpatient prescription medication use and costs in patients with diabetes have changed in a decade in Germany. A total of 46 017 patients with diabetes and 46 017 age- and sex-matched controls in 2004 were compared with 29 956 patients with diabetes and 13 226 controls in 1994. The mean annual number of prescriptions per drug-treated patient was higher in patients with diabetes than in controls, with little change over time. Prescription costs were in general about 30–50% higher for most of the drug groups in 2004 than in 1994. The annual prescription costs per patient with diabetes was about 560 € in 2004, equaling a 60% (standardized) increase from the

year 1994. The average cost of diabetes drugs increased 100% over time, and with respect to medication other than diabetes drugs, a 40% increase was observed. The increase was mainly due to cardiovascular and lipid-lowering drugs. In 2004, insulin and analogues accounted for about 22% of the drug costs and oral antidiabetic drugs for about 8% of total costs (in 1994, the corresponding numbers were 17% and 6%). In 2004, new drugs (i.e. insulin, glitazones, glinides) accounted for 15% of the total costs. In that study, the majority of the patients had type 2 diabetes, as only those over 30 years of age were included. Notably, prescription costs were assessed using the manufacturer's selling prices, which were about 50% of the pharmacy sales prices.

In a retrospective study, Currie et al. (348) estimated the costs of primary care prescribing and consultations in patients with type 1 and type 2 diabetes, with a matched cohort of people without diagnosed diabetes in the UK over a 10-year period (1997–2007). The second aim of the study was to characterize the pattern of treatment efficacy in terms of the main vascular disease risk factors: glycaemia, hypertension and lipidaemia. Data were obtained from the Health Information Network, including about 300 UK practices. The database contained information on all medical diagnoses and prescribed medications as well as laboratory values and BP readings. A total of 11 300 patients with type 1 diabetes (8.9%) and 114 752 patients with type 2 diabetes were identified from the database.

The overall mean prescribing costs per year increased markedly: by 77% (from £573 to £1014) in patients with type 1 diabetes and by 89% (from £391 to £740) in patients with type 2 diabetes from 1997 to 2007. The rate of increase was lower for the matched control subjects, 35% and 61%, respectively. The diabetes-specific costs (including the costs of glucose lowering and monitoring) represented 58% of the prescribing costs in patients with type 1 diabetes and 20% of the costs in patients with type 2 diabetes. During the follow-up, in patients with type 1 diabetes, the mean HbA_{1c} remained static since it decreased by only 0.1% (from 8.8% in 2001 to 8.7% in 2007), representing a 1% improvement. In the same time period, the systolic BP decreased from 135 to 131 mmHg and diastolic BP from 77 to 76 mmHg, representing a 5% improvement, and total cholesterol decreased from 5.4 to 4.6 mmol/L, representing a 25% improvement. The use of antihypertensive and lipid-lowering drugs increased substantially during the follow-up (from 8% to 85% in patients with type 1 diabetes and from 8% to 29% in controls).

To sum up, all of the studies described above compared the use and costs of medication between patients with diabetes and non-diabetic controls. The cross-sectional studies showed that the costs and prescribing rates of medications were higher in patients with type 1 diabetes than in controls, even when the diabetes medications were excluded. Moreover, two longitudinal studies illustrated how the average costs of medications have increased in patients with diabetes over time. However, none of the studies assessed the drug use and costs according to the predefined disease stage and diabetic complications. Also, longitudinal studies of medication use and costs of type 1 diabetes are rare, especially in Finland. Therefore, the present study focused on identifying subgroups of patients, stratified by complication status, and on clarifying major cost drivers with the intent of improving understanding of the cost structure of diabetes care.

Table 5. Summary of prescription medication costs and diabetes drug costs in patients with diabetes.

Study	Year	Country	Study design/ setting	Cohort	N	Prescription medication costs (per patient per year)	Diabetes drug costs (per patient per year)
Bruno et al. (16)	2003–2004 (12 months)	Italy	Population- based	Type 2 diabetes	32 093	828 € / 542 € ¹	278 € ¹
				Type 1 diabetes	1704	888 € / 846 € ¹	
				All diabetes Non-diabetic controls	33 797	831 € / 672 € ¹	
Reunanen et al. (17)	1995	Finland	Population- based	Type 2 diabetes	863 876	183 € / 170 € ¹	\$466
				Type 2 diabetes Non-diabetic matched controls	68 717	\$1151	
Rathmann et al. (18)	1994 and 2004	Germany	Primary care	Non-diabetic matched controls	68 717	\$366	\$790
				Type 1 diabetes	16 955	\$1272	
				Non-diabetic matched controls	16 955	\$101	
Currie et al. (348)	1997–2007	United Kingdom	Primary care	All diabetes	29 956	373 € ²	75 € ² 143 € ²
				1994	29 956	559 € ²	
				2004	46 017		
				Non-diabetic matched controls	13 226	147 € ²	
				1994 2004	46 017	210 € ²	
Currie et al. (348)	1997–2007	United Kingdom	Primary care	Type 2 diabetes	114 752	1997 / 2007 £391 ³ / £740	1997 / 2007 £77 ³ / £209
				Non-diabetic matched controls	114 752	£225 ³ / £362	
				Type 1 diabetes	11 300	£573 ³ / £1014	
				Non-diabetic matched controls	11 300	£100 ³ / £135	

¹ age- and sex-standardized; ² manufacturer's selling prices; ³ adjusted to 2007 prices

3 AIMS OF THE STUDY

As health care resources are limited, elucidating and containing the costs of diabetes care are of vital societal importance. Patients with type 1 diabetes at different disease severity stages are more likely to require different levels of resources. Therefore, it is important to identify potential subgroups of patients and major cost drivers in order to improve understanding of the cost structure of diabetes care.

There is strong evidence that guideline-based care can improve patient outcomes, and implementation of diabetes guidelines has been found to be cost-effective. Hence, it is crucial to analyse the extent to which target values of the ADA guidelines are met in normal clinical settings and how achievement of the most relevant targets affect the prognosis of the patients. These factors have a decisive role in use and cost of medication.

Specific aims of the study were as follows:

- I. To examine the 11-year cumulative cost of prescription medications according to the presence of severe complications (ESRD, MVD) and duration of diabetes.
- II. To assess trends in prescription medication use and costs by various stages of DN (normo-, micro- and macroalbuminuria) before the development of ESRD.
- III. To evaluate trends in prescription medication use and costs in two different kidney transplant cohorts.
- IV. To estimate BP control, antihypertensive treatment and prevalence of RH according to the various stages of DN.
- V. To investigate how the ADA treatment targets of HbA_{1C}, BP and LDL-C had been met, and whether these achievements have had any impact on the risk of CVD events and all-cause mortality.

4 SUBJECTS AND STUDY DESIGN

All patients analysed in this study are part of the nationwide, multicentre, ongoing Finnish Diabetic Nephropathy Study (FinnDiane) with the main aim of identifying genetic, clinical and environmental risk factors for diabetic complications among patients with type 1 diabetes. The study was launched in 1997 and to date approximately 4800 individuals have been recruited from 92 centres all over Finland (**Figure 3 A**), including all 5 university central hospitals, all 16 central hospitals, most of the regional hospitals (28/33) and 43 primary health care centres. Type 1 diabetes was defined by age at onset of diabetes < 40 years and C-peptide deficiency ≤ 0.3 nmol/L or initiation of insulin treatment within one year of the diabetes diagnosis if C-peptide was not measured.

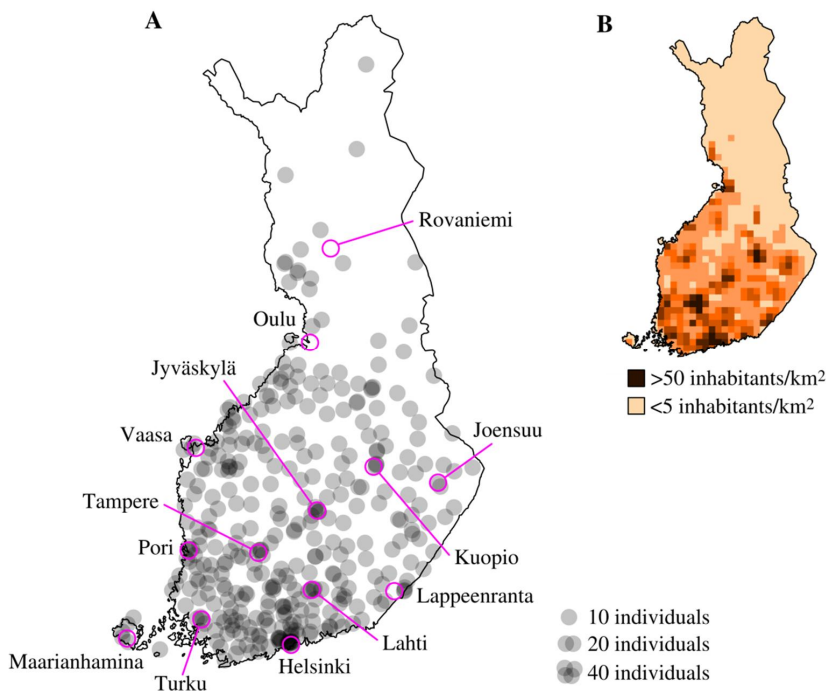


Figure 3. Geographical distribution of the FinnDiane patients (**A**) and the regional population density in Finland (**B**) (data from Statistics Finland). The figure is modified from Mäkinen (351).

The data include about 10% of adult patients (≥ 18 years old) with type 1 diabetes in Finland, and the geographical distribution of the patients is similar to the distribution of the Finnish background population (**Figure 3 B**). All adult patients with type 1 diabetes were recruited regardless of the duration of diabetes or the presence of complications, and hence, had an equal probability to participate. The local ethics committees have approved the study protocol, and the study was carried out in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients participating in

the study. Besides an ongoing baseline phase of the study, a prospective phase was launched in 2004, covering about 1600 patients' follow-up visits. Moreover, data were also obtained from the medical files and various national registers, namely the Care Register for Health Care (HILMO), the Causes of Death Register, the Drug Reimbursement Register (DRR) and the Drug Prescription Register (DPR). Study designs and clinical characteristics of the type 1 diabetes patients in each study are presented in *Table 6*.

4.1 Study I

This longitudinal prospective study comprised 3717 patients diagnosed with diabetes before 1998. Mean age of the patients was 39.1 ± 11.4 years, mean duration of diabetes 30.9 ± 11.4 years and 51% were men. Patients were divided into four complication status groups: neither MVD nor ESRD, MVD only, ESRD only or both MVD and ESRD. Data on MVD and progression to ESRD were retrieved from follow-up visits, medical files or the Causes of Death Register for all patients until the end of the year 2008. The FinnDiane data were linked to the DPR in order to obtain information on all purchases of outpatient prescription medications between 1998 and 2008. Annual and 11-year cumulative costs were calculated according to the presence of complications as well as duration of diabetes, divided into 10-year duration groups of diabetes in 1998 (0–9, 10–19, 20–29, 30–39 and ≥ 40 years).

4.2 Study II

In this prospective study, we included a total of 1905 type 1 diabetes patients, 47% of whom were men. Mean age of the patients was 39.8 ± 11.9 years and mean duration of diabetes 19.4 ± 11.1 years. All patients diagnosed before 1995 for whom complete data were available on renal status between 1995 and 2005 were included. In 1995, based on AER, patients were divided into three groups: normoalbuminuria, microalbuminuria and macroalbuminuria. Patients with ESRD were excluded. Purchases of drugs were obtained from the DPR and information on co-morbidities from several national registers: from the HILMO, the Causes of Death Register, the DRR and the DPR. The criterion for co-morbidity was a consistent diagnosis across the data sources. In this study, we estimated longitudinal trends (1995–2005) in the outpatient prescription medication use and costs by various stages of DN prior to ESRD. We compared annual cost levels and time effect, as well as profiles of medication between all three renal status groups. If the patient had progressed to the higher albuminuria level, she/he contributed data to the corresponding albuminuric category.

4.3 Study III

Data on 330 patients with type 1 diabetes (mean age 42.5 ± 8.4 years and mean duration of diabetes 30.4 ± 7.9 years; 62% men) and cadaveric kidney transplant until 2008 were obtained from the FinnDiane database. Patients were typically hospitalized three to four weeks after the operation and the drugs dispensed during the hospital stay were not recorded in any registers. Therefore, the patients were followed for a maximum of nine years after the first month of transplantation. In this study, the use and costs of prescription medication between the earlier (transplanted 1986–1999, $n=180$) and the later (transplanted 2000–2008, $n=150$) transplant cohorts were compared. All purchases of outpatient prescription drugs were obtained from the DPR between 1995 and 2009. Data on co-morbidities were obtained until 2009, as described before. The main focus was to estimate overall trends in diabetes, immunosuppressive and other drugs (other than diabetes or immunosuppressive drugs) in both transplant cohorts. Moreover, immunosuppressive regimens were compared between the cohorts.

4.4 Study IV

This cross-sectional study included 3678 patients with type 1 diabetes with complete data on systolic and diastolic BP as well as on nephropathy status. Mean age of the patients was 38.0 ± 12.0 years and mean duration of diabetes 22.1 ± 12.3 years. About 51% of the patients were men. The baseline data were collected between 1995 and 2008. About 60% had their baseline visit before 2000. For all patients, results are shown according to two different BP targets: $< 130/85$ mmHg, which was the ADA target until 2000, and $< 130/80$ mmHg, which was the target between 2001 and 2013. Patients were divided into five nephropathy status groups: normo- ($n=2370$), micro- ($n=488$) and macroalbuminuria ($n=526$) as well as dialysis ($n=123$) and kidney transplantation ($n=171$).

The FinnDiane data were linked to the DPR in order to obtain information on the purchases of antihypertensive medication used in outpatient care six months prior to the baseline visit. Patients were further divided into groups based on whether they had reached the BP targets or not and whether the antihypertensive medication was used or not at baseline. Uncontrolled BP was defined as failure to reach the BP target despite the use of antihypertensive treatment, whereas RH was defined as failure to reach the BP target, even after using a minimum of three antihypertensive drugs from different classes, one of which was a diuretic. In this study, we also estimated the factors related to RH.

4.5 Study V

In this prospective study, we included 3151 patients with type 1 diabetes (mean age 37.1 ± 11.6 years, mean duration of diabetes 21.1 ± 11.8 years, 49.9% men) for whom we had complete data on HbA_{1C}, systolic and diastolic BP and LDL-C. The baseline data were collected between 1995 and 2004. Patients were classified into two DN status groups:

those without DN (normo- or microalbuminuria) and those with DN (macroalbuminuria or ESRD). We studied whether each individual, simultaneously, had met the ADA treatment targets of HbA_{1C}, BP and LDL-C or not. Moreover, we assessed whether these target achievements had any impact on the risk of CVD events and all-cause mortality. The so-called hard CVD events (MI, revascularization procedures and stroke) were identified from the HILMO and Causes of Death Register by December 2011. All causes of deaths were obtained from the Causes of Death Register by December 2012. Information on purchases of antihypertensive and lipid-lowering drugs were obtained from the DPR six months before and after the baseline visit. A preliminary analysis, where all eight treatment achievement groups were included, showed that hypertension had an overwhelming effect on the CVD risk, as the risk did not differ between the groups in which the BP was not on target. Thus, we divided the patients into three achievement groups: at least BP on target, BP not on target and none of the three on target.

Table 6. Study designs and clinical characteristics of patients with type 1 diabetes in Studies I – V.

Study	I	II	III	IV	V
Focus of study	Medication utilization and cumulative costs by complication status	Medication utilization and cost trends by various stages of DN	Medication utilization and cost trends after kidney transplantation	Antihypertensive treatment and resistant hypertension	Treatment target achievements and risk of CVD and mortality
Study design	Longitudinal, prospective	Longitudinal, prospective	Longitudinal, prospective	Cross-sectional	Longitudinal, prospective
Follow-up	1998–2008	1995–2005	1995–2009 (9 years)	NA	until 2011–2012
N	3717	1905	330	3678	3151
Men (%)	51	47	62	51	50
Age (years)	39.1 ± 11.4	39.8 ± 11.9	42.5 ± 8.4	38.0 ± 12.0	37.1 ± 11.6
Duration of diabetes (years)	30.9 ± 11.4	19.4 ± 11.1	30.4 ± 7.9	22.1 ± 12.3	21.1 ± 11.8
Median age at diabetes onset (years)	14 (9–22)	13 (9–22)	11 (7–15)	14 (9–22)	14 (9–22)
Renal status (n)					
Normoalbuminuria	2164	1334	None	2370	2136
Microalbuminuria	469	206	None	488	437
Macroalbuminuria	555	365	None	526	428
ESRD	274	None	330	294	150
Unclassified	255	None	None	None	None
HbA _{1c} (% / mmol/mol)	8.5 ± 1.4 / 69 ± 16	8.5 ± 1.4 / 69 ± 16	8.7 ± 1.5 / 72 ± 16	8.4 ± 1.5 / 68 ± 16	8.4 ± 1.5 / 68 ± 16
Systolic BP (mmHg)	135 ± 19	135 ± 18	152 ± 23	134 ± 19	133 ± 18
Diastolic BP (mmHg)	80 ± 10	79 ± 10	86 ± 12	79 ± 10	79 ± 10
Total cholesterol (mmol/L)	5.0 ± 1.0	5.0 ± 0.9	5.4 ± 1.2	4.9 ± 1.0	4.9 ± 0.9
HDL-cholesterol (mmol/L)	1.33 ± 0.39	1.34 ± 0.39	1.18 ± 0.42	1.33 ± 0.39	1.33 ± 0.40
LDL-cholesterol (mmol/L)	3.08 ± 0.94	3.06 ± 0.85	3.49 ± 1.03	3.04 ± 0.87	3.06 ± 0.87
Median triacylglycerol (mmol/L)	1.04 (0.77–1.48)	1.01 (0.76–1.41)	1.54 (1.11–2.22)	1.02 (0.77–1.46)	1.01 (0.76–1.43)
BMI (kg/m ²)	25.1 ± 3.5	25.2 ± 3.5	24.5 ± 3.7	25.0 ± 3.5	24.9 ± 3.5
Waist circumference (cm)	86.0 ± 11.3	85.6 ± 11.2	88.6 ± 12.1	85.5 ± 11.3	84.9 ± 10.9
Current smoking (%)	23	22	22	24	25
Died during follow-up, n (%)	370 (10)	123 (6.5)	98 (30)	NA	302 (10)
Antihypertensive medication (%)	41	40	94	38 (37 ¹)	34 (36 ¹)
Lipid-lowering medication (%)	13	12	32	12	8 (11 ¹)

Unless stated otherwise the numbers in columns are means ± SD, ¹Data from the Drug Prescription Register

5 METHODS

5.1 FinnDiane Study protocol

At each participating study centre, patients were recruited by nurses and physicians. Baseline and prospective visits were carried out according to the same protocol. During the visits, the patients underwent a thorough clinical investigation that took place in conjunction with a regular visit. Details of clinical characteristics of patients, including age at diagnosis, insulin therapy and diabetic complications, were obtained from the medical records by the physician using a standardized questionnaire. During the visit also BP and anthropometric variables were measured. Moreover, blood samples were drawn after a light breakfast for subsequent assays, and urine collections were performed for the measurement of the AER. In addition, each participant completed a detailed questionnaire on life-style, smoking habits and family history. Finally, information on all purchases of prescription medication was obtained from the national DPR and data on co-morbidities from several registers, verified from medical files.

5.1.1 Anthropometric measurements and blood pressure

Weight was measured in light clothing with a standardized scale, registered to the closest 0.1 kg and height to the closest 1 cm. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured midway between the lowest rib and iliac crest and hip circumference from the widest part of the gluteal region. Waist-to-hip ratio (WHR) was calculated as waist divided by hip circumference. BP was measured twice with a two-minute interval in the sitting position after 10 minutes' rest using either a mercury sphygmomanometer or an automated standardized BP device. The mean of these two readings was used in the analyses.

5.1.2 Assessment of renal status and function

Renal status was defined on the basis of the measured AER in at least two out of three urine collections. Until November 2002, AER was determined by radioimmunoassay (Pharmacia, Uppsala, Sweden), and thereafter, by immunoturbidimetry (Hitachi 911 analyser, Roche Diagnostics, Hoffman-La Roche, Basel, Switzerland). Patients were grouped into four classes: normal AER ($\text{AER} < 20 \mu\text{g/min}$ or $< 30 \text{ mg/24 h}$), microalbuminuria ($20 \leq \text{AER} < 200 \mu\text{g/min}$ or $30 \leq \text{AER} < 300 \text{ mg/24 h}$), macroalbuminuria ($\text{AER} \geq 200 \mu\text{g/min}$ or $\geq 300 \text{ mg/24 h}$) and ESRD (i.e. dialysis or kidney transplantation).

Serum creatinine was determined (at the central laboratory) by the kinetic Jaffe reaction using a Hitachi 911 E analyser, with normal reference for males of $< 115 \mu\text{mol/L}$ and for females $< 100 \mu\text{mol/L}$, until January 2002, and thereafter, by a photometric,

enzymatic method using a Hitachi 917 or Modular analyser, with normal reference for males of 50–95 µmol/L and for females for 40–90 µmol/L. The correlation coefficient between the two methods was 0.988.

Renal function was based on eGFR. In Studies I and II, renal function was calculated by the MDRD-4 (104) and in Studies IV and V by the CKD-EPI (106) equation. On the basis of eGFR, patients were divided into five groups according to the KDOQI guidelines: Stage 1, eGFR ≥ 90 mL/min/1.73 m² (normal kidney function), Stage 2, eGFR 60–89 mL/min/1.73 m² (mildly reduced function), Stage 3, eGFR 30–59 mL/min/1.73 m² (moderately reduced function), Stage 4, eGFR 15–29 mL/min/1.73 m² (severely reduced function) and Stage 5, eGFR <15 mL/min/1.73 m² (very severe or end-stage kidney failure).

5.1.3 Glycaemic control and insulin sensitivity

HbA_{1C} was determined locally at each centre using standardized assays. Traditionally, HbA_{1C} has been reported as a percentage of total haemoglobin (Studies I–III). To ease comparisons between laboratories from different countries, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has recently recommended that HbA_{1C} concentration be reported in mmol of HbA_{1C} per mol of haemoglobin (mmol/mol). Thus, HbA_{1C} is reported as both percentages and mmol/mol in Studies IV and V.

Insulin sensitivity was determined by an equation for the estimated glucose disposal rate (eGDR) (352) modified for the use of HbA_{1C}, instead of HbA₁:

$$eGDR = 24.4 - 12.97 * WHR - 3.39 * AHT - 0.60 * HbA_{1C}$$

(AHT is 1 if patient has antihypertensive treatment and/or BP $\geq 140/90$ mmHg, otherwise 0).

5.1.4 Lipids and lipoproteins

Serum lipids and lipoproteins were measured centrally from the blood samples at the research laboratory of Professor Marja-Riitta Taskinen at the Helsinki University Central Hospital, Helsinki, Finland. Total cholesterol and triacylglycerol were determined enzymatically by a Cobas Mira analyser (Hoffman-La Roche, Basel, Switzerland) until January 2006, and thereafter, by a Konelab 60i analyser (Thermo Fisher Scientific, Waltham, MA, USA). Serum HDL-C concentrations were determined enzymatically using a HTS 7000 plus Bio Assay Reader (Perkin Elmer, Waltham, MA, USA). LDL-C was calculated with the Friedewald equation [total cholesterol - HDL-C - (triacylglycerol)/2.2] (209).

5.1.5 Definition of macrovascular disease

In Study I, macrovascular disease (MVD) was defined as the presence of coronary heart disease, acute MI, stroke, coronary revascularization and amputation. All amputations were pooled regardless of the aetiology. In Study V, the category “CVD events” denotes revascularization procedure, MI, stroke and cardiac causes of deaths.

5.2 Registers

5.2.1 Drug Prescription Register

The Social Insurance Institution has maintained the DPR since 1994. The register contains information on costs of medications prescribed, purchased and reimbursed in outpatient care. The register includes the patient’s identification code, purchase date and cost of the drug (retail price). Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) classification, based on the valid ATC index version (2009–2013). In the ATC classification system, drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties (279). Drugs are classified in groups at five levels. Drugs are divided into 14 main groups (1st level), with one pharmacological/therapeutic subgroup (2nd level). The 3rd and 4th levels are chemical/pharmacological/therapeutic subgroups, and the 5th level is the chemical substance. As an example,

ATC classification of insulin glargine (Lantus ®), **A10AE04**:

A	alimentary tract and metabolism (1st level, anatomical main group)
A10	drugs used in diabetes (2nd level, therapeutic subgroup)
A10A	insulin and analogues (3rd level, pharmacological subgroup)
A10AE	insulin and analogues, long-acting (4th level, chemical subgroup)
A10AE04	glargine insulin (5th, chemical substance)

5.2.2 Drug Reimbursement Register

Since 1964, the Social Insurance Institution has also maintained the DRP. It contains information on entitlement to full or partial special reimbursement of drug costs for certain chronic diseases, which are classified by specific reimbursement code. Fulfillment of the criteria for eligibility for special reimbursement must be proven by a certificate from the treating physician. This register provides a source for co-morbidity data on the patients suffering from some specific chronic diseases and conditions.

5.2.3 Care Register for Health Care

The Care Register for Health Care, HILMO (named the Hospital Discharge Register until 1993), maintained by the National Institute for Health and Welfare, contains all dates of hospital admissions and discharges since 1969, each patient's unique personal identifier and up to four diagnoses with the International Classification of Diseases (ICD). Moreover, in 1994, this register was expanded to cover day surgery and long-term care and in 1998 also outpatient visits to hospitals.

5.2.4 Causes of Death Register

The Causes of Death Register was established by Statistics Finland in 1936, when death certificates were issued by medical doctors systemically across the country. The statistics on causes of death are compiled from data obtained from death certificates, which are supplemented with data from the population information system of the Population Register Centre. These statistics, updated on an annual basis, include all Finnish residents who have died during the preceding year in Finland and abroad. Since 1996, the statistics have been compiled according to the 10th revision of the ICD.

5.3 Statistical methods

In all studies, the data are expressed as means with standard deviation (SD) for normally distributed variables, as medians with interquartile range for non-normally distributed values and as percentages. Differences between groups for normally distributed variables were tested by using ANOVA, for non-parametric data using the Kruskal-Wallis test or the Mann-Whitney *U* test and for categorical variables using Pearson's chi-square (χ^2) test or two-tailed Fisher's exact test, as applicable. All analyses in Studies I–III were performed using SAS 9.2 version and in Studies IV and V using the SAS 9.3 version (SAS Institute Inc., Cary, NC, USA). A *P* value of < 0.05 was considered significant.

Because some patients incurred markedly high medication costs, the distribution of the costs was asymmetrically skewed to the right, which is a typical distribution for health care costs. Therefore, in Study I, generalized linear mixed models (GLMM) under gamma distribution and log link (353) were used to evaluate the 11-year cumulative costs and covariates associated with these costs. The medication costs were adjusted to 2008 or 2009 euro levels by using the Consumer Price Index (CPI, obtained from the Statistics Finland). The GLMM framework allows fitting of correlated data under the non-normal distribution assumption. Gamma distribution was chosen to remove heteroscedasticity in the error variances (i.e. capacity to fit errors that are distributed differently from the normal) and to achieve precise estimates (354). Moreover, the GLMM framework allows grouping medication costs into discrete time intervals and takes into account the different follow-up time of each patient during the study period. The cost data were presented as least-square means with 95% CI (i.e. the LSMEANS statement in the PROC GLIMMIX procedure).

In Study I, separate models were applied for those without (neither MVD nor ESRD) and with complications (MVD only, ESRD only, both MVD and ESRD). The costs in the models were adjusted for age, sex, BMI and contributing years (i.e. patients' follow-up years from 1998 until death or end of the follow-up by December 2008). In addition, all variables with a P value of < 0.05 were included in the final multivariate models (duration of diabetes, total insulin dose/day, complication status, contributing years of MVD and ESRD). The GLMM framework is also appropriate for repeated measures. Therefore, the GLMM under gamma distribution and log link were used to explore time trends and differences in medication costs by renal status groups during the period between 1995 and 2005 (Study II) as well as the medication costs nine years after kidney transplantation in two different transplant cohorts (Study III). The annual average cost estimates were produced based on the above-mentioned LSMEANS statement.

In Study II, the annual costs of medications were adjusted for age, sex, BMI, hospital days, contributing years (from 1995 to 2005) and mortality (alive on 31 December 2005) as well as for co-morbidities (asthma, cancer, mental disorders, neurological diseases and rheumatoid arthritis), as applicable. Before this adjustment, in an additional analysis the total cost of medication was deflated by using the Wholesale Price Index (WPI) for medicines. Statistics Finland prepares the WPI for medicines upon request, submitting it to Pharma Industry Finland on an annual basis. The calculation of the index is based on wholesale prices of medications that have been on the market for at least two years. Thus, the index represents trends in wholesale prices (pharmaceutical companies' and wholesalers' share of the prices) of the medications. However, as shown in **Table 2**, the retail prices are an approximately linear transformation of wholesale prices. The results of this additional analysis are shown later, but not in the original study II.

In Study III, the costs were adjusted for age at the time of kidney transplantation, sex, transplantation year, mortality as a dummy variable (alive or dead on 31 December 2009, alive=1, dead=0), hospital days after kidney transplantation and re-entry to dialysis as well as co-morbidities [asthma and chronic obstructive disease (COPD), cancer, mental disorders, neurological diseases (epilepsy, multiple sclerosis, Parkinson's disease), cardiovascular disease (ischaemic heart disease and stroke) and rheumatoid arthritis], as applicable.

In Study IV, a multivariate logistic regression analysis was applied using a stepwise selection procedure to test which variables were independently associated with RH. The studied predictors were sex, age, HbA_{1C}, insulin dose, laser treatment, triacylglycerol, HDL cholesterol, presence of CHD, nephropathy status, waist-to-hip-ratio, eGFR and 24-h urinary sodium excretion rate. Results are presented as odds ratios with 95% CI.

Finally, in Study V, the 10-year cumulative incidence of CVD events and all-cause mortality was analysed by the Kaplan-Mayer method according to the three achievement groups in those without and with DN, as well as when patients were classified into four stages of renal function (Stages 4 and 5 pooled together). The log-rank test was used to evaluate differences between achievement groups. The data were further analysed by Cox regression models, which provide hazard ratios (HRs) with 95% CI for the development of CVD event and death. The multivariate models were adjusted for duration of diabetes, sex, eGFR, waist-to-hip ratio and use of antihypertensive medication.

6 RESULTS

6.1 Use and costs of prescription medication (I-III)

6.1.1 Complication status and cumulative costs of medication (I)

Approximately a one-quarter of the patients had severe diabetic complications: about 10% had MVD only, 6% had ESRD only and 7% suffered from both MVD and ESRD. In general, patients with complications were older, had longer duration of diabetes and were more often men. As might be expected, they also had higher BP, worse dyslipidaemia and poorer glycaemic control than those without MVD and ESRD. They also had lower eGFR and insulin dose per day. Patients with ESRD had an earlier onset of diabetes. About three-quarters of the patients with complications died during the follow-up, but the mortality rate was the highest (~50%) among those with both MVD and ESRD. The observed annual costs per patient were 1000 € in those without complications, 1600 € in those with MVD only, 8000 € in those with ESRD only and 7500 € in those with both MVD and ESRD.

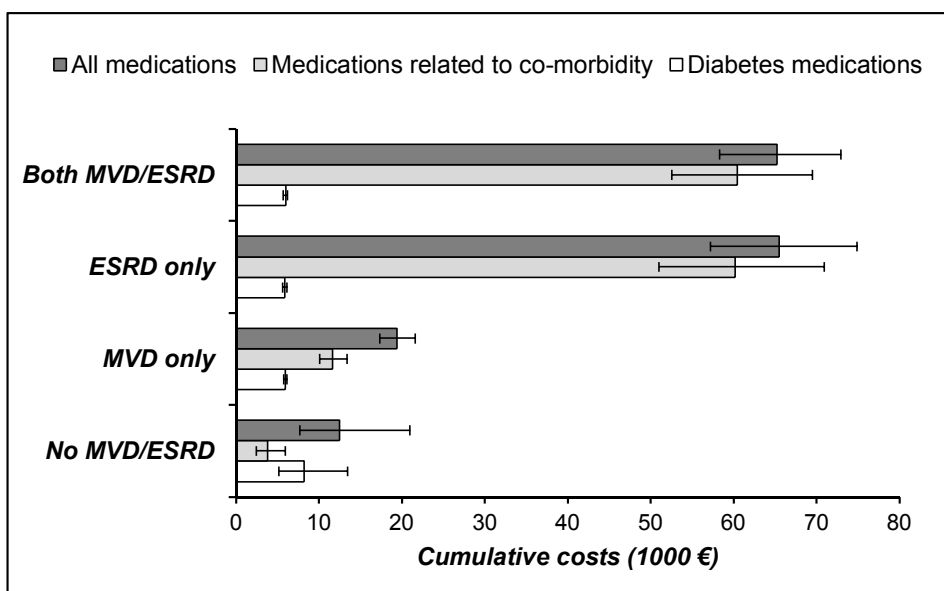


Figure 4 Eleven-year cumulative cost of diabetes medication, medication related to co-morbidity and all medications (deflated to 2008 euro levels by using the CPI) in patients with type 1 diabetes by complication status. Data are presented as least-square means with 95% CI (gamma GLMM). Costs were adjusted for age, sex, BMI, complication status and contributing years of follow-up time. In addition, diabetes medication costs were adjusted for total insulin dose/day, cost of medications related to co-morbidity for duration of diabetes and contributing years of ESRD and all medication costs for total insulin dose/day and contributing years of ESRD.

The least-square mean 11-year cumulative costs of prescription medication were 56% higher in patients with MVD, but increased fourfold when ESRD was present or both MVD and ESRD were present, compared with the cost of the patients without any complications (*Figure 4*). Although the costs of diabetes medication were stable regardless of complication status, the medication costs related to co-morbidity increased significantly according to the complication status group, being up to 15 times higher in patients with both MVD and ESRD (3800 € vs. 60 500 €).

Figure 5 depicts the proportions of the cumulative costs by different types of medications in each complication status group. Diabetes medication accounted for almost three-quarters of the total cost for patients without MVD or ESRD, whereas the corresponding proportion was 40% for patients with MVD only and about 8% for patients with ESRD or both complications. Cardiovascular medications were the second highest contributor to the total costs (30%) in those with MVD only, while the proportion was 12% for patients without complications, 7% for patients with ESRD only and 9% for patients with both MVD and ESRD. Immunosuppressive drugs accounted for 28% and peritoneal dialytics for 28% of the total costs in the group with ESRD only. With both MVD and ESRD, the proportions were 33% and 27%, respectively. Notably, the share of EPO was 10% of the total costs if ESRD was present.

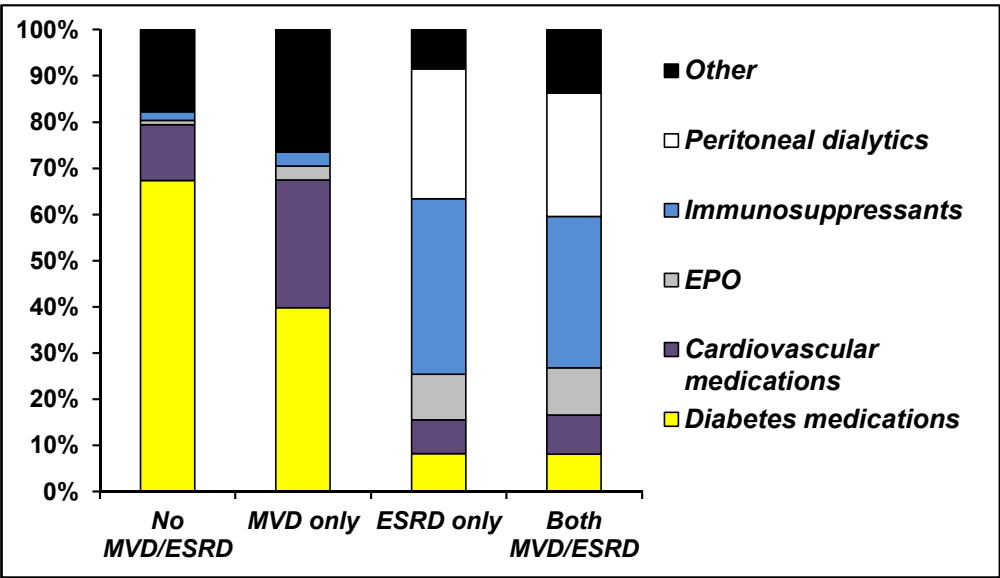


Figure 5. Proportions of the 11-year cumulative costs of different types of medication according to the complication status in patients with type 1 diabetes.

6.1.2 Duration of diabetes and cumulative costs of medication (I)

To determine how duration of diabetes affects cumulative costs, the patients were divided into five 10-year duration groups in 1998 within each complication status group. Notably,

when ESRD was present the adjusted least-square mean cost of diabetes medication was lower (5050–5820 €) and the cost of medication related to co-morbidity was substantially higher (63 060–68 770 €) in all 10-year duration groups, compared with patients without complications (corresponding numbers 7890–8580 € and 2470–4740 €). However, duration of diabetes had only a minor effect on the costs within each complication status group. Those without complications and with the shortest duration of diabetes (0–9 years) had slightly higher cost of diabetes medication (8580 € vs. 7930 €, $P = 0.01$) and lower cost of medication related to co-morbidity (2470 € vs. 4180 €, $P = 0.05$) than those with the longest duration (≥ 40 years). Similarly, patients with MVD and shorter duration of diabetes (10–19 and 20–29 years) had higher cost of diabetes medication (7610 € vs. 6150 €, $P = 0.0001$ and 6740 € vs. 6150 €, $P = 0.03$) than those who had had diabetes for 40 years or more.

6.1.3 Trends in use and costs of medication by various stages of DN before the development of end-stage renal disease (II)

At the beginning of the follow-up, about 70% ($n = 1334$) of the patients had normal AER, while 10% ($n = 206$) belonged to the microalbuminuria and 20% ($n = 365$) to the macroalbuminuria group. During the follow-up 12% of normoalbuminuric, 45% of microalbuminuric and 37% of macroalbuminuric patients progressed to a higher level of albuminuria or ESRD. The mean follow-up time was 10.8 (± 0.9) years, and 123 patients died during the follow-up.

6.1.3.1 Total cost of medication

The total cost of medication increased in all groups over time (**Figure 6**). The average annual increase in the normoalbuminuria group was 3.5%, in the microalbuminuria group 3.3% and in the macroalbuminuria group 5.2%. Also cost levels differed significantly between the groups ($P < 0.0001$). In 1995, the annual costs per patient were 1310 € (95% CI 1230–1400) in those with normal AER, 1450 € (1300–1600) in those with microalbuminuria and 1770 € (1620–1930) in those with macroalbuminuria. In 2005, the corresponding figures were 1950 € (1830–2080), 2110 € (1910–2320) and 2900 € (2650–3180). Of note, the increase levelled off during the last year of follow-up. Moreover, the cost profiles differed between the groups (interaction between group and time: $P = 0.04$). As seen in **Figure 6**, the cost profile in the macroalbuminuria group diverges from the other two groups over time.

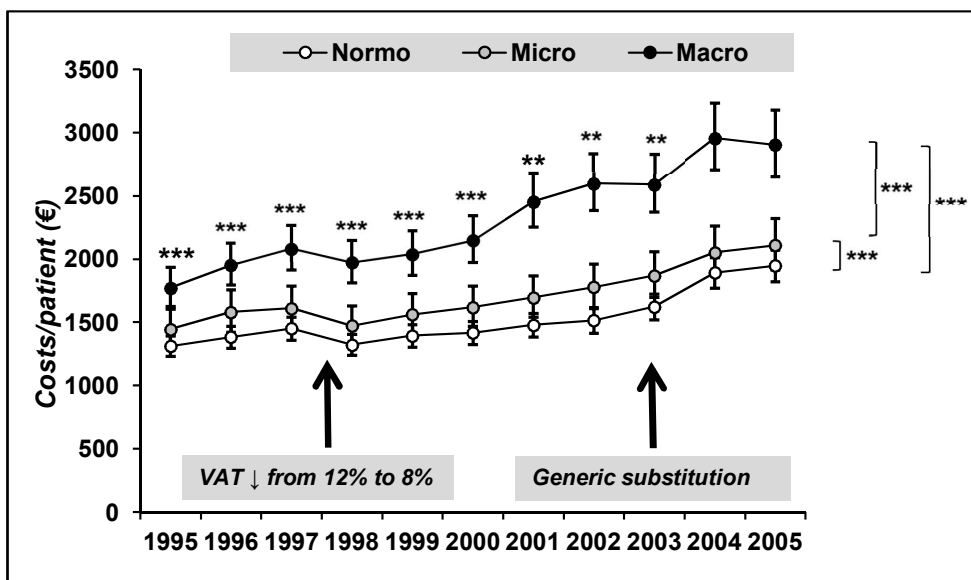


Figure 6. Annual cost trends (least-square means with 95% CI, gamma GLMM) of all prescription medication (deflated to 2009 euro levels by using the CPI) according to the different stages of DN in patients with type 1 diabetes. Costs were adjusted for age, sex, renal status, contributing years of follow-up time, BMI, hospital days and mortality (alive in 2005) as well as for co-morbidities [asthma and COPD, cancer, mental disorders, neurological diseases (Parkinson's disease, MS, epilepsy) and RA]. $P < 0.01$ **, $P < 0.001$ *** (reference year 2005).

As expected, the total costs of medication were substantially lower when the WPI for medicines was used to deflate the costs (**Figure 7**) relative to deflation with the CPI (**Figure 6**); on average, the costs were about 35% lower using the WPI instead of the CPI in all three nephropathy status groups. However, the trends of the total costs were similar irrespective of the index used; medication costs increased over time in all groups ($P < 0.0001$), and cost levels ($P < 0.0001$) and cost profiles (interaction between group and time: $P = 0.04$) differed significantly between the groups.

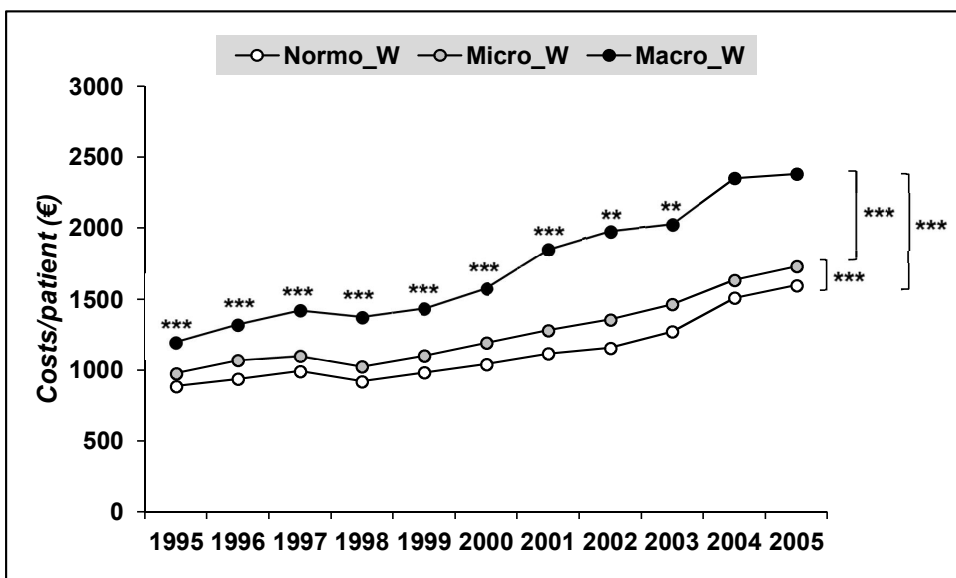


Figure 7. Annual cost trends (least-square means with 95% CI, gamma GLMM) of all prescription medication (deflated to 2009 euro levels by using the WPI for medicines) according to the different stages of DN in patients with type 1 diabetes. Costs were adjusted for age, sex, renal status, contributing years of follow-up time, BMI, hospital days and mortality (alive in 2005) as well as for co-morbidities [asthma and COPD, cancer, mental disorders, neurological diseases (Parkinson's disease, MS, epilepsy) and RA]. $P < 0.01$ **, $P < 0.001$ *** (reference year 2005). (Lithovius et al. unpublished results).

6.1.3.2 Diabetes medication

Figure 8 shows the costs of diabetes medication according to the renal status groups. Between 1995 and 1997, the costs increased annually by 2.9% ($P < 0.0001$). As expected, the costs decreased in 1998 due to the VAT reduction. Thereafter, the costs were constant for four years, until a rapid increase occurred between 2002 and 2004 (by 12.9% annually, $P < 0.0001$). No differences were observed in cost profiles between the groups (interaction between group and time: $P = 0.99$). However, the cost was slightly lower in the macroalbuminuria group than in the normo- ($P = 0.002$) or microalbuminuria ($P = 0.0007$) groups. The share of the diabetes medication of the total cost changed over time. In patients with normal AER, the share was over 80% in 1995, but it decreased to 65% in 2005. The corresponding numbers were 73% and 62% for patients with microalbuminuria and 50% and 40% for patients with macroalbuminuria.

6.1.3.3 Cardiovascular medication

Cardiovascular drugs were the second highest contributor to total costs in the micro- and macroalbuminuric patients. The cost share has increased over time in all groups: from

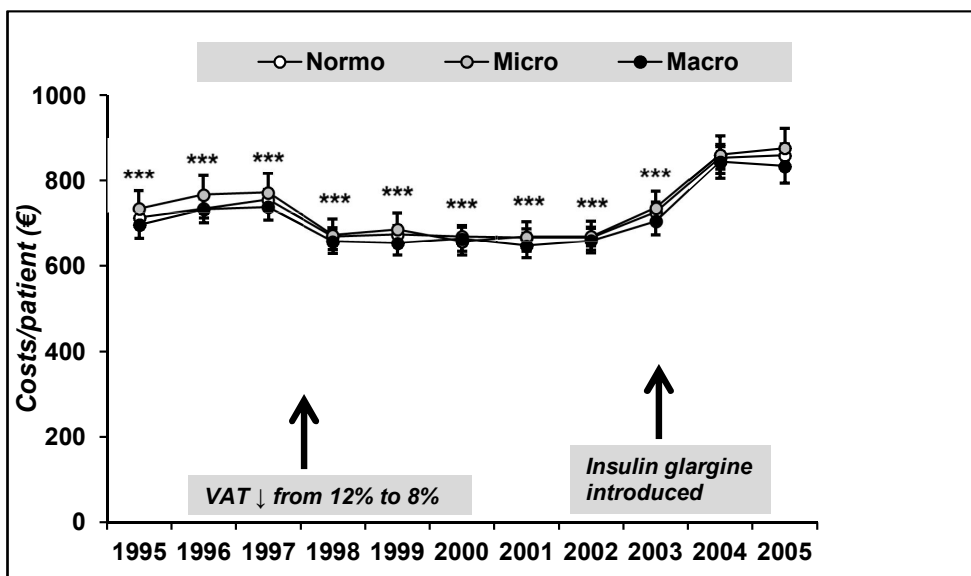


Figure 8. Annual cost trends (least-square means with 95% CI, gamma GLMM) of diabetes medication (deflated to 2009 euro levels by using the CPI) by different stages of DN in patients with type 1 diabetes. Costs were adjusted for age, sex, renal status, contributing years of follow-up time, BMI, hospital days and mortality (alive in 2005). $P < 0.001$ *** (reference year 2005).

11% to 40% among normoalbuminuric, from 49% to 74% among microalbuminuric and from 81% to 94% among macroalbuminuric patients. The most commonly used cardiovascular medications were agents acting on the RAAS and lipid-modifying drugs.

Figure 9 presents the costs of agents acting on the RAAS and lipid-modifying drugs by renal status groups, as well as the proportions of patients who had purchased these drugs during the follow-up. Although the costs of both drugs ($P < 0.0001$) were higher in patients with macroalbuminuria than in the other groups, no differences were observed between the normo- and microalbuminuria groups. The costs of the agents acting on the RAAS decreased slightly (by 2.8% annually) until 2002, but thereafter the decrease speeded up, being on average 9.9% per year. With regard to lipid-modifying agents, the costs were rather constant until 2001, but then the costs began to decline sharply (by 12.6% annually). Interestingly, at the same time, the consumption of both drugs increased in all renal status groups. The proportion of the patients who purchased agents acting on the RAAS increased from 6% to 27% in patients with normal AER, from 42% to 66% in microalbuminuric patients and from 69% to 87% in macroalbuminuric patients over time. The consumption of lipid-modifying drugs increased from 0% to 20% among normoalbuminuric patients, from 1% to 32% among microalbuminuric patients and from 12% to 57% among macroalbuminuric patients. Thus, the consumption of these drugs was also the highest in patients with macroalbuminuria.

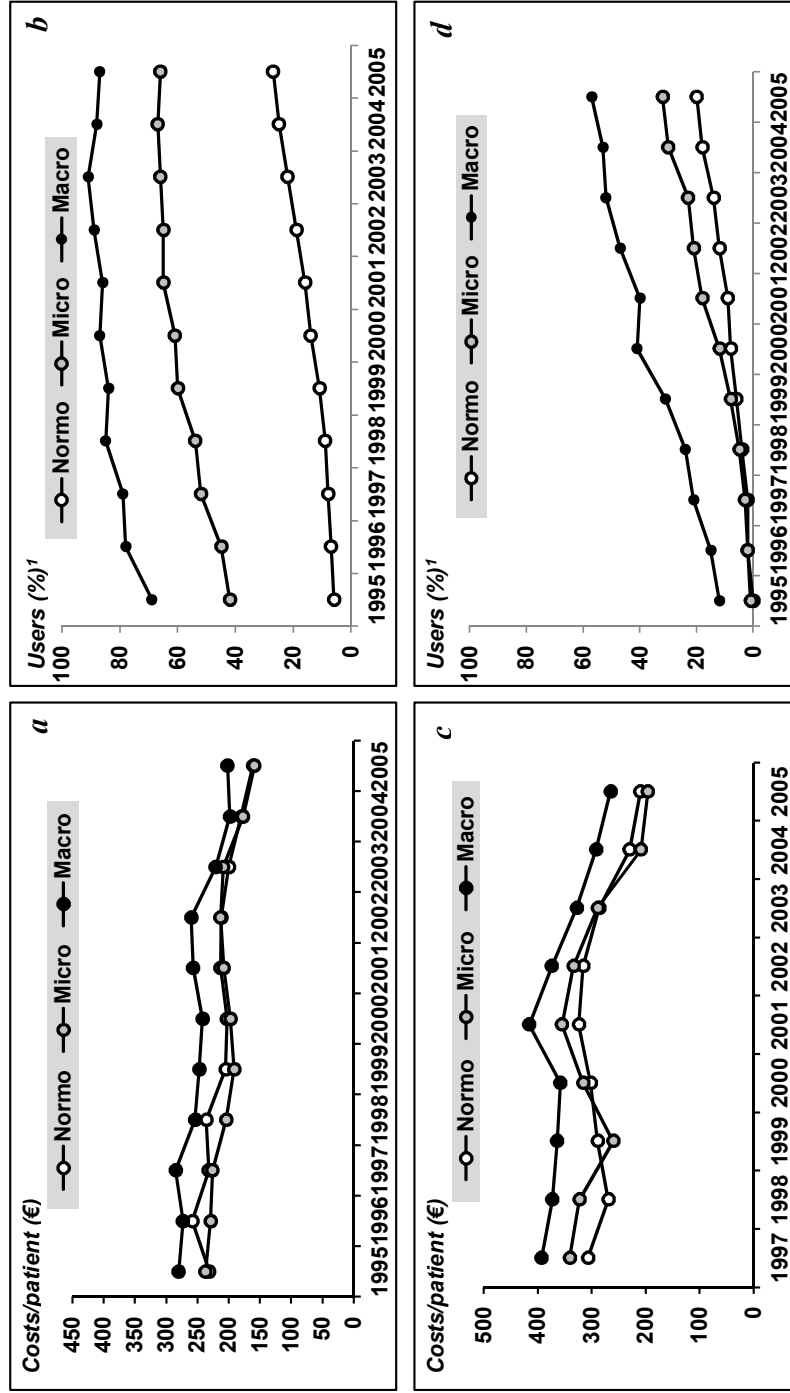


Figure 9. Annual costs trends (deflated to 2009 euro levels by using the CPI) of agents acting on the renin-angiotensin-aldosterone system [ATC C09] (a) and users (b), as well as the annual cost trends of lipid-modifying agents [ATC=C10] (c) and users (d). Costs were adjusted for age, sex, contributing years of follow-up time, BMI, hospital days, renal status and mortality (alive in 2005). ¹At least one purchase from the medication class during the year.

6.1.4 Trends in use and cost of medication after kidney transplantation (III)

In general, the patients from the earlier cohort (transplanted in 1986–1999) were younger at the time of transplantation than the patients from the later cohort (transplanted in 2000–2008). Obviously, due to a longer follow-up time, they were also more likely to re-enter dialysis, had more hospital days and had a higher mortality rate.

6.1.4.1 Costs of medication

Total annual costs of medication per patient decreased from 11 290 € to 8760 € in the earlier cohort and from 12 800 € to 9790 € in the later cohort during the follow-up ($P < 0.0001$). **Figure 10** shows the cost trends of immunosuppressive, diabetes and other drugs according to the two transplant cohorts. The cost profiles of immunosuppressive drugs were similar ($P = 0.9$), showing decreasing trends in both cohorts. The decrease was the steepest between the first and the second year; the cost decreased by 16.8% in the earlier cohort and by 6.4% in the later cohort. The cost was higher in those transplanted after the millennium ($P < 0.0001$), although the gap narrowed towards the end of the follow-up. The costs of diabetes drugs decreased in both cohorts at the beginning of the

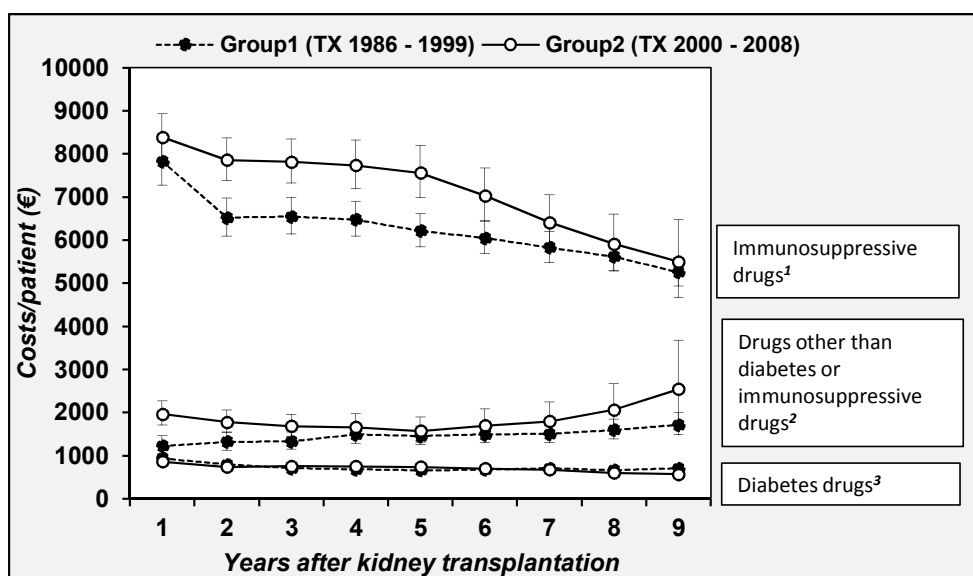


Figure 10. Annual cost trends (least-square means with 95% CI, gamma GLMM) of immunosuppressive drugs, diabetes drugs and drugs other than diabetes or immunosuppressive drugs (deflated to 2009 euro levels by using the CPI) in patients with type 1 diabetes nine years after kidney transplantation in two different transplant cohorts. The costs were adjusted for age at kidney transplantation, sex, transplantation year and hospital days after transplantation.

¹ In addition, costs adjusted for mortality (alive on 31 December 2009) and re-entry to dialysis.

² In addition, costs adjusted for re-entry to dialysis. ³ In addition, costs adjusted for mortality (alive on 31 December 2009).

follow-up, but stabilized thereafter. The costs of other drugs were higher in the later cohort ($P < 0.0001$), but no differences were observed in the cost profiles ($P = 0.3$) or annual costs per patient over time ($P = 0.09$). On the whole, the effect of diabetes and other drugs on the total costs was minor.

6.1.4.2 Immunosuppressive regimen

Figure 11 depicts the proportion of different immunosuppressive regimens during the nine-year follow-up by transplant cohort. This figure illustrates how the immunosuppressive regimens have changed over time. The most common regimen was the combination of cyclosporine, azathioprine and corticosteroid in the earlier cohort, while the combination of cyclosporine, mycophenolate mofetil (MMF) and corticosteroid prevailed in the later cohort. Notably, in those who were transplanted in 2000 and thereafter the use of steroids decreased considerably during follow-up, and the combination of cyclosporine and MMF became more common. Almost all patients had purchased steroids during the first year of follow-up. In the earlier cohort, about 80% of patients had steroids in the regimen during the following years, while in the later cohort the proportion was approximately 40%. About one-quarter of the patients from the later cohort had purchased tacrolimus during the first seven years. The corresponding proportion was less than 10% in those who had transplantation before 2000. The average cost of the combination of cyclosporine and azathioprine was 4900 € (95% CI 4760–5040), cyclosporine and MMF 9030 € (8770–9300) and tacrolimus and MMF 8860 € (8470–9260). Thus, the costs were substantially higher when MMF rather than azathioprine was in the regimen ($P < 0.0001$).

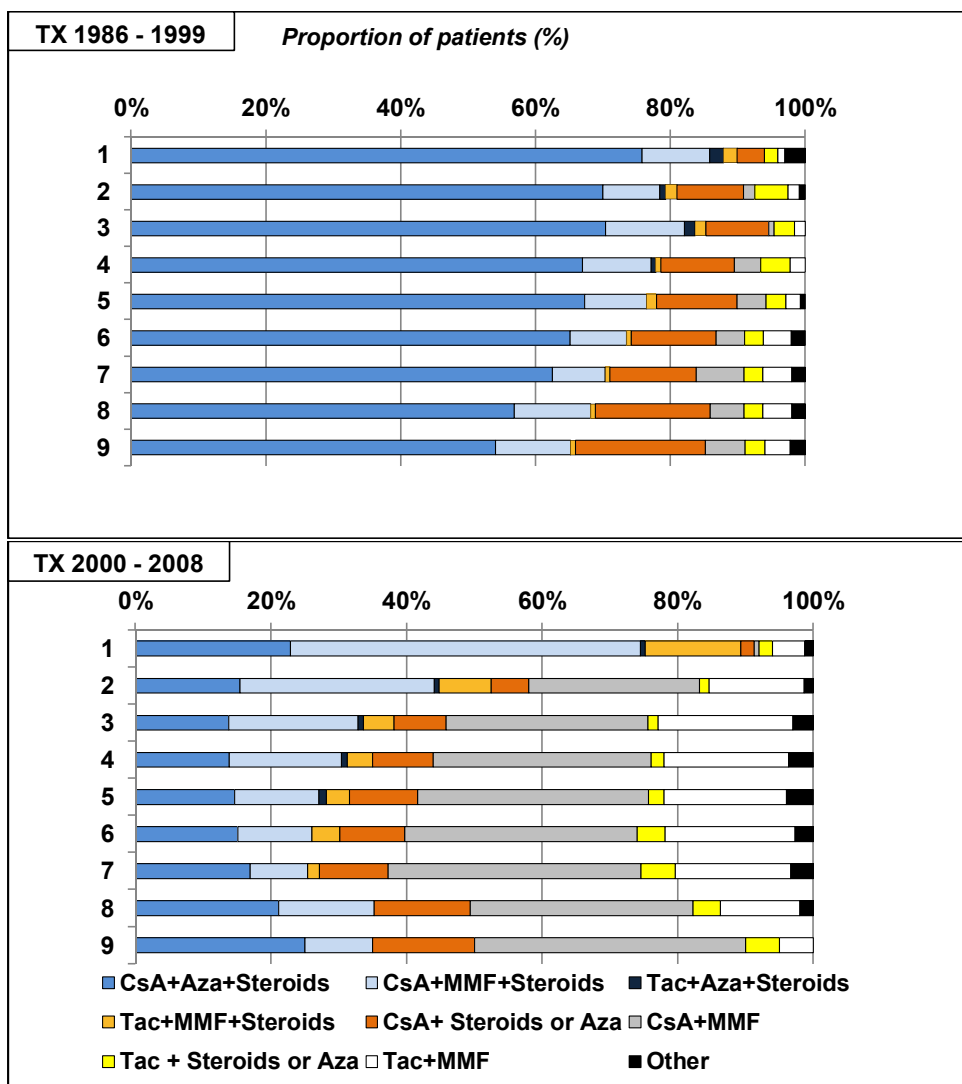


Figure 11. Immunosuppressive regimens in patients with type 1 diabetes nine years after kidney transplantation in two different transplantation cohorts. TX=kidney transplantation, CsA=cyclosporine, Aza=azathioprine, MMF= mycophenolate mofetil, Tac=tacrolimus.

6.2 Diabetes guidelines: Implementation of recommendations (IV, V)

6.2.1 BP control and antihypertensive treatment by stages of DN (IV)

Of all patients, 60.9% had not reached the BP target of < 130/85 mmHg (target until 2000) and 70.3% the target of < 130/80 mmHg (target between 2001 and 2012) at baseline. The patients who failed to reach the targets were older, had longer duration of diabetes and were more often men. They also had poorer glycaemic and lipid control and more micro- and macrovascular complications. About 37% of all patients had antihypertensive treatment.

As illustrated in **Figure 12 a**, the numbers of patients with antihypertensive treatment and the prevalence of uncontrolled hypertension varied greatly between the DN status groups. In patients with normoalbuminuria, about 14% were on antihypertensive treatment, and with regard to the target of < 130/85 mmHg nearly 75% of them had uncontrolled BP. The corresponding numbers were 61% and 71% for patients with microalbuminuria, 90% and 80% for patients with macroalbuminuria, 89% and 88% for patients with dialysis, and 91% and 90% for patients with transplantation. The numbers were obviously worse with the target of < 130/80 mmHg, but the trend was similar (**Figure 12 b**).

Figure 13 shows the number of antihypertensive drugs in use. The figure illustrates the division of those who reached and those who failed to reach the target into different groups with regard to the number of drugs. Notably, 58% of patients with normal AER who had not reached the BP target, and 61% of the patients with microalbuminuria were taking only one antihypertensive drug (**Figure 13 a, b**). On the other hand, more than half of the dialysis and 40% of macroalbuminuric and transplanted patients who failed to reach the BP target had at least three drugs in their regimen (**Fig. 13 c, d, e**). Almost all patients with antihypertensive treatment had an ACE inhibitor or an ARB in their regimen.

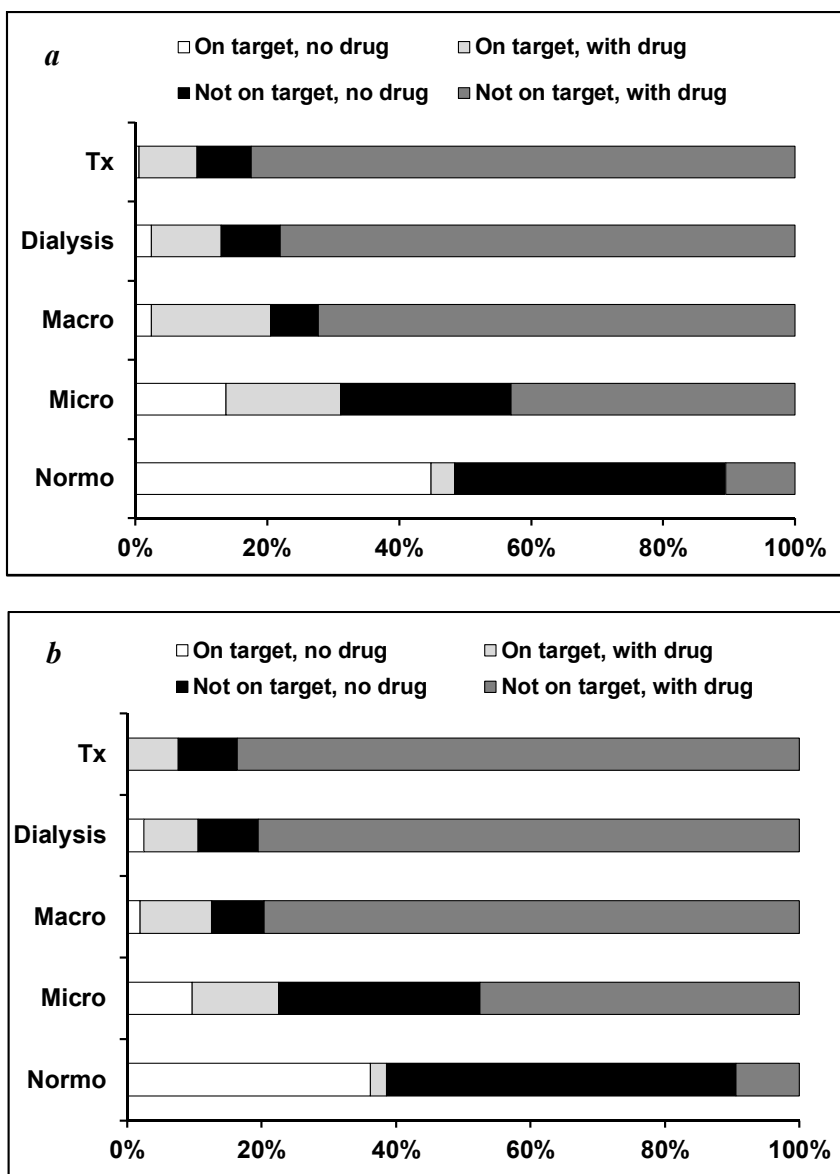


Figure 12. Blood pressure control based on the ADA BP target < 130/85 mmHg (a) and < 130/80 mmHg (b) in patients with type 1 diabetes according to the different stages of DN. Tx, kidney transplantation.

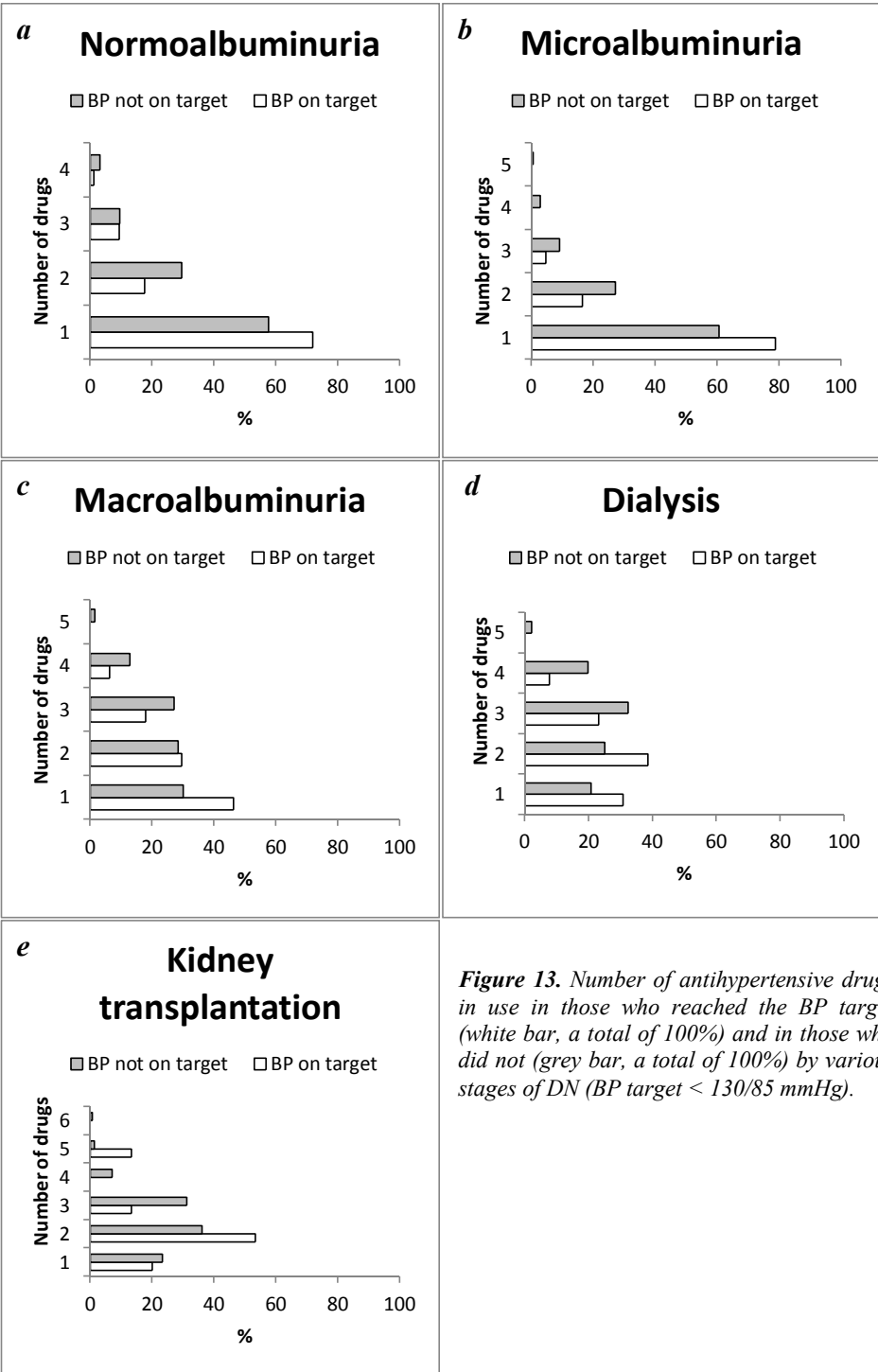


Figure 13. Number of antihypertensive drugs in use in those who reached the BP target (white bar, a total of 100%) and in those who did not (grey bar, a total of 100%) by various stages of DN (BP target < 130/85 mmHg).

6.2.2 Resistant hypertension (IV)

The prevalence of RH (failure to achieve the target BP [$< 130/85$ mmHg] after using ≥ 3 antihypertensive drugs from different classes, one of which is a diuretic) was 7.9% for all patients with type 1 diabetes and 21.2% among the antihypertensive drug-treated patients (**Figure 14**). However, the prevalence of RH increased alongside the worsening of DN (**Figure 15**). In the normoalbuminuria group, the prevalence was 1.2% of all and 8.7% of drug-treated patients. The corresponding numbers were 4.7% and 7.8% for microalbuminuric patients, 28.1% and 31.2% for macroalbuminuric patients, 36.6% and 41.3% for patients on dialysis and 26.3% and 28.8% for kidney-transplanted patients.

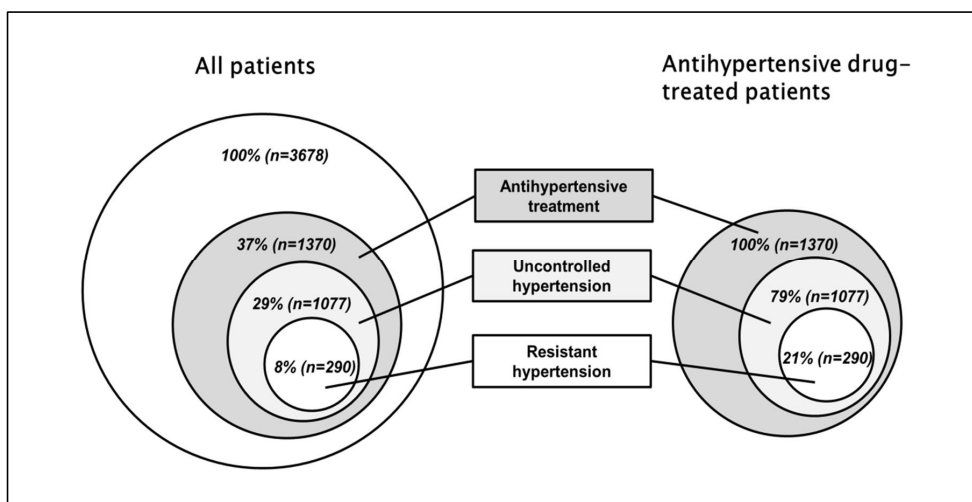


Figure 14. Prevalence of uncontrolled and resistant hypertension (BP $\geq 130/85$ mmHg) of all and antihypertensive drug-treated patients with type 1 diabetes.

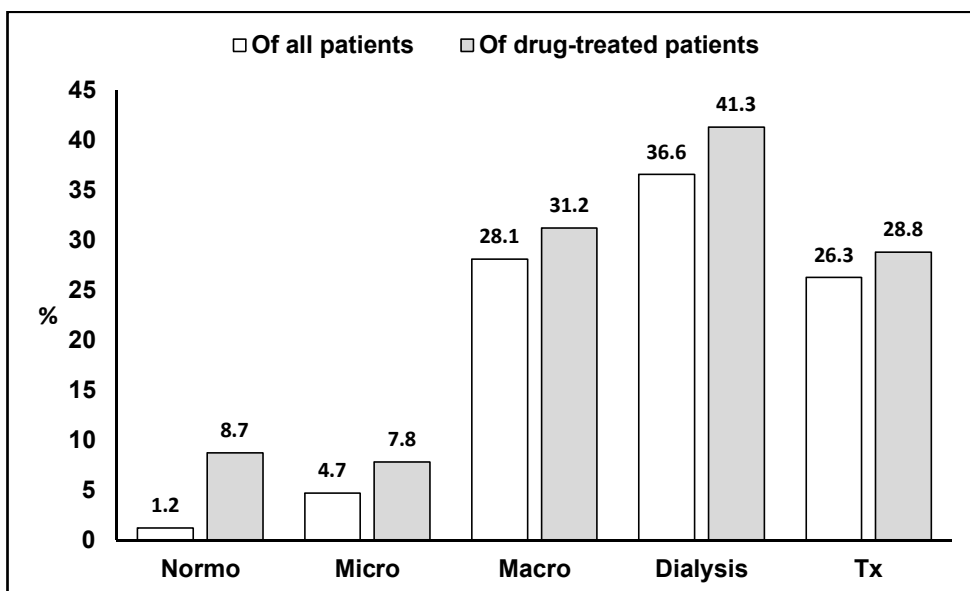


Figure 15. Prevalence of RH (BP \geq 130/85 mmHg) of all (white bars) and antihypertensive drug-treated (grey bars) patients with type 1 diabetes according to the different stages of DN.

Table 7 demonstrates that higher age, lower eGFR, higher waist-to-hip ratio, higher triacylglycerol and micro- and macroalbuminuria were independently associated with RH (Model 1). Moreover, 24-h urinary sodium rate was measured in a subset of the patients. Thus, an additional analysis showed that dietary sodium intake was also independently associated with RH (Model 2).

Table 7. Variables independently associated with RH in patients with type 1 diabetes.

Model 1 (N=3384)		
Variable	OR (95% CI)	P value
Age (years)	1.04 (1.02–1.05)	< 0.0001
eGFR (mL/min/1.73 m ²)	0.97 (0.96–0.97)	< 0.0001
Normoalbuminuria	1.0	-
Microalbuminuria	2.58 (1.43–4.67)	0.002
Macroalbuminuria	5.61(3.20–9.84)	< 0.0001
WHR (per one-tenth increase)	1.44 (1.15–1.80)	< 0.0001
Triacylglycerol (mmol/L)	1.19 (1.01–1.40)	0.04
Model 2 (N=2203)		
Variable	OR (95% CI)	P value
Age (years)	1.04 (1.02–1.07)	< 0.0001
eGFR (mL/min/1.73 m ²)	0.96 (0.95–0.98)	< 0.0001
Normoalbuminuria	1.0	-
Microalbuminuria	2.86 (1.37–5.95)	0.005
Macroalbuminuria	6.93 (3.54–13.54)	< 0.0001
Triacylglycerol (mmol/L)	1.22 (1.01–1.49)	0.04
24-h sodium excretion rate (mmol/24 h; per 10 units increase)	1.05 (1.02–1.09)	0.002

Stepwise multivariate logistic regression analysis. Predictors in the model: sex, age, HbA_{1C}, insulin dose, laser treatment, triacylglycerol, HDL-C, presence of CHD, nephropathy status, WHR, eGFR and 24-h urinary sodium excretion rate. Dialysis and kidney transplantation patients were excluded.

6.2.3 Glycaemic, BP and lipid control and prognosis of patients (V)

6.2.3.1 Achievements of HbA_{1C}, BP and LDL cholesterol

At baseline, a total of 2136 normo- and 437 microalbuminuric patients were classified into the group without DN, and 428 macroalbuminuric and 150 ESRD patients into the group with DN. Thus, altogether 18% of the patients had DN. There were 333 CVD events during 33 707 person-years, with a median of 11.2 (IQR 9.6 – 13.0) years of follow-up, and 302 deaths during 34 917 person-years, with a median of 11.4 (IQR 10.1 – 13.1) years. **Table 8** shows all eight achievement groups. Notably, less than 4% of the patients without DN and only one person with DN had achieved the ADA treatment targets of HbA_{1C}, BP and LDL-C, simultaneously. By contrast, 34% of those without DN and 63% of those with DN had failed to reach all three targets.

Table 8. Achievements of HbA_{1C}, BP and LDL-C targets¹ based on ADA guidelines in patients with type 1 diabetes according to the prevalence of DN, situation at baseline.

HbA _{1C}	BP	LDL-C	No DN n (%)	DN n (%)	P value	All n (%)
			2573 (81.7)	578 (18.3)	< 0.0001	3151 (100)
+	+	+	99 (3.9)	1 (0.2)	< 0.0001	100 (3.2)
+	+	–	116 (4.5)	11(1.9)	0.004	127 (4.0)
+	–	+	66 (2.6)	11 (1.9)	0.4	77 (2.4)
–	+	+	365 (14.2)	25 (4.3)	< 0.0001	390 (12.4)
+	–	–	106 (4.1)	25 (4.3)	0.8	131 (4.2)
–	+	–	578 (22.5)	72 (12.5)	< 0.0001	650 (20.6)
–	–	+	368 (14.3)	69 (11.9)	0.1	437 (13.9)
–	–	–	875 (34.0)	364 (63.0)	< 0.0001	1239 (39.3)

¹HbA_{1C}<7% (<53 mmol/mol), BP <140/80 mmHg, LDL-C <2.6 mmol/L. A plus (+) indicates that the target has been reached and a minus (–) that it has not.

About half of the patients without DN and nearly one-third of the patients with DN had achieved one of the three targets (**Figure 16**). In addition, one-fifth of the patients without DN and only 8% of the patients with DN had reached two of the three targets. About 15% of the patients without DN and 8% of the patients with DN had HbA_{1C} below 7%. The corresponding proportions of the patients who achieved the BP target of < 140/80 mmHg were 45% and 19%. Finally, 35% and 18% had reached the LDL-C target of < 2.6 mmol/L.

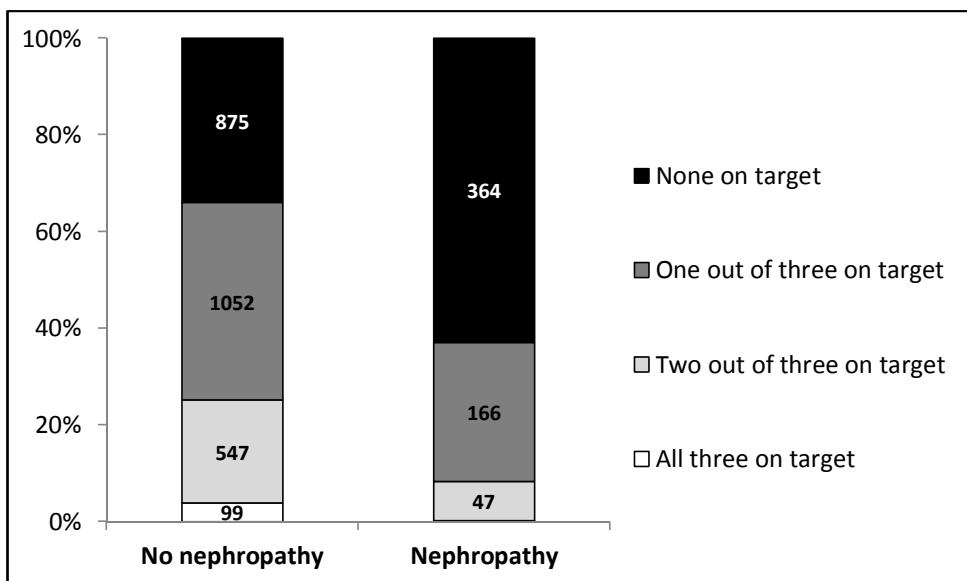


Figure 16. Achievements of treatment targets in patients with type 1 diabetes according to the prevalence of DN, situation at baseline. Cut-off values: HbA_{1C} < 7%, BP < 140/80 mmHg and LDL-C < 2.6 mmol/L.

6.2.3.2 Ten-year risk of cardiovascular disease

Without DN, the 10-year cumulative risk of CVD was 3.8% (95% CI 2.7 – 4.8) for those who had at least BP on target at baseline, 4.4% (2.7 – 6.2, $P = 0.3$) for those whose BP was not on target and 8.1% for those who reached none of the targets. The corresponding shares with DN were 17.4% (95% CI 11.1 – 23.2), 29.9% (23.0 – 36.2, $P = 0.03$) and 28.4% (24.9 – 31.8, $P = 0.009$) (**Figure 17**). Among the patients with DN, the CVD risk was 90% higher if BP was not on target [HR 1.9 (95% CI 1.1 – 1.3)] and increased twofold if none of the targets were met [HR 2.2 (1.4 – 3.6)], compared with those who had at least BP on target after adjustments for duration of diabetes, sex, eGFR, waist-to-hip ratio and use of antihypertensive medications (**Table 9**). No significant differences were observed in the risk between the achievement groups without DN. However, the Cox regression model showed borderline significance in those who failed to reach all three targets [HR 1.44 (0.99 – 2.09), $P = 0.06$].

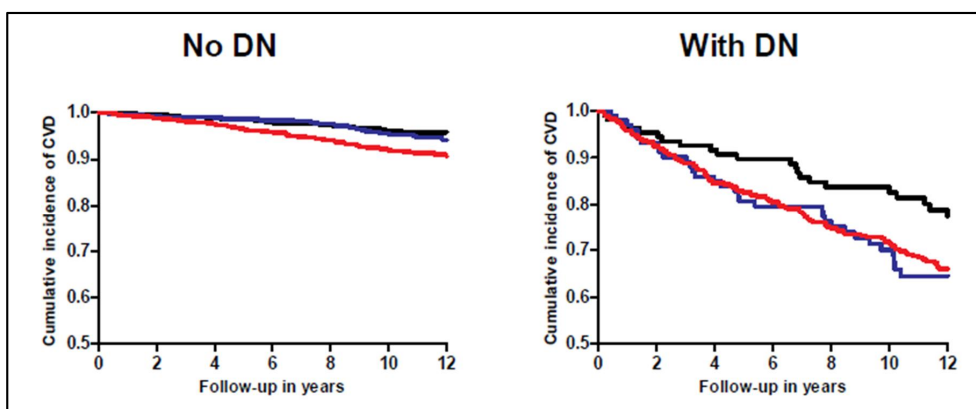


Figure 17. Ten-year cumulative risk of CVD event in patients with diabetes without and with DN according to the three achievement groups: all three targets met or at least BP in control (black line), BP not on target (blue line), none of the three on target (red line). Treatment targets: $HbA_{1C} < 7\%$ (< 53 mmol/mol), $BP < 140/80$ mmHg, $LDL-C < 2.6$ mmol/L.

6.2.3.3 Ten-year risk of all-cause mortality

Figure 18 illustrates the risk of all-cause mortality in both DN status groups. In those without DN, the risk was 2.9% (95% CI 2.0 – 3.9) if BP was on target, 2.7% (1.3 – 4.1, $P = 0.9$) if BP was not on target and 5.3% (3.8 – 6.7, $P = 0.003$) if none of the targets had been reached. The corresponding figures with DN were 18.4% (95% CI 12.2 – 24.1), 27.9% (21.4 – 33.9, $P = 0.4$) and 27.1% (23.6 – 30.3, $P = 0.3$). In those with DN, after adjustment no differences were seen between the three achievement groups (**Table 9**). Even though the risk of death without DN was higher in those who failed to reach all three targets, after adjustment no differences were observed between the groups.

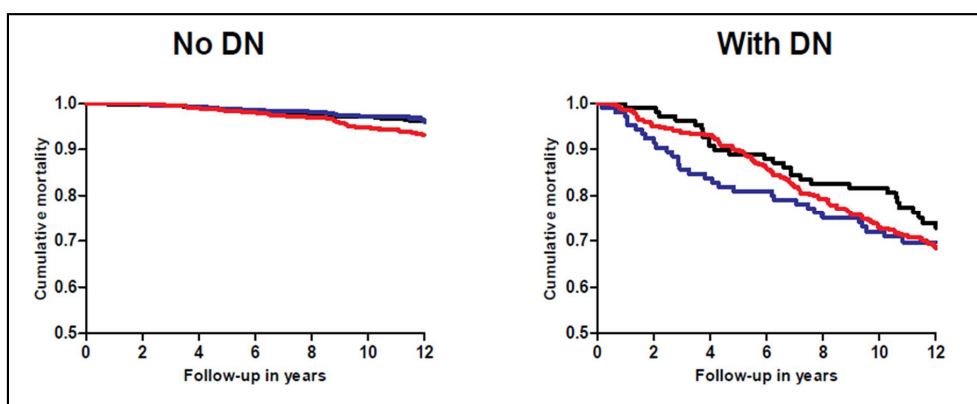


Figure 18. Ten-year cumulative risk of all-cause mortality in patients with diabetes without and with DN according to the three achievement groups: all three targets met or at least BP in control (black line), BP not on target (blue line), none of the three on target (red line). Treatment targets: $HbA_{1C} < 7\%$ (< 53 mmol/mol), $BP < 140/80$ mmHg, $LDL-C < 2.6$ mmol/L.

Table 9. Cox regression models for CVD events and all-cause mortality in patients without and with DN.

CVD event	No DN	DN
Variable	HR (95% CI), <i>P</i>	HR (95% CI), <i>P</i>
BP in control	1.0	1.0
BP not in control	0.96 (0.59–1.56), 0.9	1.93 (1.11–3.33), 0.02
Failed to reach all three targets	1.44 (0.99–2.09), 0.06	2.22 (1.38–3.56), 0.001
Duration of diabetes (years)	1.08 (1.06–1.09), < 0.0001	1.06 (1.04–1.08), < 0.0001
Male sex	1.11 (0.72–1.71), 0.6	1.10 (0.76–1.60), 0.6
eGFR (ml /min/1.73 m ²)	0.99 (0.98–1.00), 0.2	0.98 (0.98–0.99), < 0.0001
Waist-to hip ratio (per one-tenth increase)	1.29 (1.00–1.67), 0.05	1.18 (0.95–1.47), 0.1
Antihypertensive treatment	1.93 (1.36–2.73), 0.0002	0.92 (0.50–1.71), 0.8
All-cause mortality	No DN	DN
Variable	HR (95% CI), <i>P</i>	HR (95% CI), <i>P</i>
BP in control	1.0	1.0
BP not in control	0.96 (0.95–0.98)	1.16 (0.70–1.90), 0.6
Failed to reach all three targets	1.18 (0.77–1.80), 0.4	1.20 (0.79–1.81), 0.4
Duration of diabetes (years)	1.06 (1.04–1.07), < 0.0001	1.01 (1.01–1.05), 0.003
Male sex	0.92 (0.56–1.50), 0.7	1.27 (0.87–1.85), 0.2
eGFR (ml /min/1.73 m ²)	1.00 (0.98–1.01), 0.4	0.98 (0.98–0.99), < 0.0001
Waist-to hip ratio (per one-tenth increase)	1.60 (1.05–2.14), 0.001	1.45 (1.17–1.80), 0.0007
Antihypertensive treatment	1.57 (1.05–2.36), 0.03	0.96 (0.52–1.77), 0.9

7 DISCUSSION

Overall, the findings from the large nationwide FinnDiane Study presented in this thesis highlight the importance of early intervention to prevent or delay diabetic kidney disease in patients with type 1 diabetes. Although diabetes itself generates high medication costs, the progression to more severe stages of DN increases the costs dramatically, even before the development of ESRD. Another important finding is that the prevalence of uncontrolled and resistant hypertension is a common problem in patients with advanced renal disease. It is, however, important to emphasize that glycaemic, BP and lipid control are also suboptimal among those without or with early signs of diabetic complications. In addition, evidence suggests that successful implementation of the treatment targets of HbA_{1C}, BP and LDL-C proposed by the ADA would be useful for the optimal prevention of CVD and mortality in patients with type 1 diabetes.

7.1 Utilizing national registers

For research purposes, Finland offers several comprehensive and high-quality register databases maintained by the National Institute for Health and Welfare, the Social Insurance Institution and Statistics Finland. Data collection and utilization are regulated by legislation that ensures individuals' rights to privacy and confidentiality. The system of unique identification codes enables not only linking of person-level data across different administrative registers, but also combining of register data with various observational study designs, such as retrospective cohort studies with longitudinal or cross-sectional study designs (355). Even though these registers are established for administrative practices and needs, they have good coverage and validity and a large dataset can be obtained at relatively low costs (356). With careful study planning and by transforming the data from the original registers to a suitable form for research purposes, these registers provide an excellent resource for investigating medication utilization and costs. To create a more comprehensive overview of the longitudinal trends in prescription medication use and costs, information from the large validated population-based DPR has been combined with data collected in the FinnDiane Study.

For the purposes of this thesis, the same individual's purchases of drugs could conveniently be collected retrospectively from the DPR database, and it was possible to create a longitudinal record for her/him. Combining register data allows tracking and comparing of changes in utilization of medication over time in different subgroups (e.g. in patients with type 1 diabetes by various stages of DN). It is also possible to search drugs from the register under special classes and create longitudinal figures (such as immunosuppressive regimens in two different transplant cohorts) or to identify patients who have purchased certain drugs (such as the use of antihypertensive medications prior to baseline by stages of DN).

To obtain information on co-morbidities, several independent sources were utilized: the HILMO, the DRR and the DPR (Studies II, III and V). The first register refers to inpatient information, while the others are sources of outpatient information. Moreover,

within the FinnDiane Study, self-reported data on several co-morbidities, including rheumatoid arthritis, asthma, depression and epilepsy, were collected by questionnaires. In addition, data on mortality, including time and causes of deaths, were obtained from Statistics Finland, which maintains the national archive of death certificates. To ensure a high level of ascertainment, we cross-linked all of these data sources, and the criterion for a diagnosed co-morbidity was that there was no inconsistency across the different data sources used. In approximately 90% of the cases, information on a particular co-morbidity was found in at least two data sources. In addition, from the HILMO we were able to calculate hospital days for each patient during the study period.

7.2 Strengths and limitations of the study

The main strength of this project is the large sample size and the longitudinal study design. All participants in the five studies are part of the nationwide, multicentre, prospective FinnDiane Study, which includes about 10% of all Finnish adult patients with type 1 diabetes. All patients with type 1 diabetes were formerly treated at hospitals' outpatient clinics. In recent years, however, many adult patients with type 1 diabetes, especially without severe complications, have been transferred to the primary health care units. To avoid sampling bias, the FinnDiane Study population is recruited from all levels of the health care system: from primary health care to university central hospitals, and it covers patients with different severity stages of disease. It is also noteworthy that although the FinnDiane Study is not, by strict definition, population-based, a selection bias is unlikely as the geographical distribution of the patients is similar to the general distribution of inhabitants in Finland. Moreover, the study population is well-characterized regarding clinical factors, medical history and classification of diabetic complications.

The main focus in this thesis was to investigate the prescription medication costs and use in outpatients with type 1 diabetes over time. As discussed above, data collected from the DPR allow the creating of longitudinal records of medication use and costs. Nevertheless, the costs of medications obtained from the DPR explain only a part of the total health care costs and about three-quarters of the total sales of medications. Nearly all over-the-counter medications and all medications dispensed during hospital stay or stay in other institutional care units are not recorded in the DPR. Notably, in contrast to peritoneal dialytics, haemodialysis fluids are mainly administered by the hospital and not registered in the DPR. Unfortunately, it is difficult to obtain accurate data on inpatient costs at the patient level, as such data are not available from any national database. The only way to obtain such data would be to examine the costs of every patient separately from the medical files, which would not necessarily be accurate, especially when assessing longitudinal trends. The risk of hospitalization and death typically increases with advanced renal disease. Thus, the results presented in this thesis may underestimate the actual use and cost of medications. To minimize bias, these confounders have been controlled (mortality, hospital days) in multivariate models.

Although the coverage and accuracy of the DPR are high, only reimbursed medications are recorded in the register. As described above, the costs of medicinal products are

reimbursed only after the holder of the marketing authorization has applied for reimbursement and a reasonable wholesale price from the PPB. The Board can also restrict the basis for reimbursement to a precisely defined diagnosis or severity stage of the disease. Moreover, several legislative measures have affected the content and coverage of the DPR. The fixed deductible rate per purchase was abolished in 2006. Thus, inexpensive drugs which did not reach the limit are missing up to 2006, but thereafter are recorded in the register. Since 2007, medications funded by the employer are also documented in the register. Since all patients have been affected by the above-mentioned changes in the same way, it is likely that these changes have only a minor effect on the results.

Notably, the real doses and frequencies of the use of drugs are not available from the DPR. Instead, the Defined Daily Doses (DDD) calculated from the volume of sales of pharmacies and hospitals by wholesalers and from the assumed theoretical average doses per day for each patient have been included in the register (277). Thus, the DDD is only a rough estimate of the consumption (i.e. technical expedient, which is not necessarily equal to the real dose of drug) and therefore is only suitable for studying consumption of the drugs on the population level (277). Therefore, we did not use that imprecise variable, but identified the number and classes of medications purchased (from the desired time period), providing more relevant estimates than DDD for the purposes of this study. Nevertheless, it is important to bear in mind that some medications sold may be unused by the patient.

In the current study, the medication costs were deflated (either to 2008 or 2009 euro levels) by using the CPI. The index has frequently been used in drug studies and is recommended by the Social Insurance Institution (279). The CPI describes the price development of goods and services purchased in Finland by household residents. The CPI, as a general measure of inflation, is calculated with a method in which the prices of different commodities are weighed as shares of consumption using the Laspeyres' price index formula. However, the weight of medicines is marginal, as the weight of health care overall is only 5% and medicines form only a proportion of this. In addition, the prices of reimbursable medicines are in the index net of reimbursement, which means that the consumer prices of 100% reimbursable diabetes medicines are zero plus a small co-payment (Statistics Finland).

As described above, in order to keep medication prices at a reasonable level, the prices of pharmaceuticals are regulated by law in Finland and in other European countries. Generic substitution and the reference price system as well as the cut in wholesale prices have reduced the prices of reimbursable medications, despite the simultaneous increase in taxes and patients' co-payments for these drugs. It is therefore well-founded to contemplate the use of indices other than the CPI in analysing the trends in drug costs.

An additional analysis shows substantially lower costs of medications when the costs were deflated by using the WPI for medicines. As described earlier, the index is based on wholesale prices of medications that have been on the market for at least two years. The calculation of the index follows Fisher's price index formula. The recent index material consists of the price data of approximately 6000 drug packages. In 2013, about 76% of drugs sold in Finland were included in the calculation (Nadia Tamminen, Pharma Industry Finland, 8.1.2015). As presented in **Table 2**, the retail price of the drug includes the shares of the manufacturer and wholesaler, the pharmacy's margins and taxes. In 2012, the

combined share of the pharmaceutical company and wholesaler was about 60% of the retail price, while the proportion of the pharmacy was about 25% and the proportion of the state about 15% (<http://www.pif.fi>).

As the CPI and the WPI for medicines have developed in opposite directions (<http://www.pif.fi>), it is probable that our results overestimated the actual costs of medications. In contrast, by using the WPI for medicines the costs would have been underestimated, as the WPI represents the trends in wholesale prices (pharmaceutical companies' and wholesalers' share of the prices) of the medications, but not the overall trends in drug costs. Despite these shortcomings, the drug costs increased with worsening of renal disease, already before the development of ESRD. Irrespective of which index is used, the trends remain the same. However, to avoid these biases in the future, it would be desirable to develop a Retail Price Index for medicines for research purposes.

7.3 How does progression of DN affect medication use and costs (I, II)?

Results from Study I show that the presence of MVD and ESRD increases the 11-year cumulative cost of outpatient prescription medication substantially in patients with type 1 diabetes. Notably, the impact of renal failure on the costs is enormous. In Finland (Finnish Kidney Register) and other countries (88), the prevalence of ESRD among patients with type 1 diabetes is about 1–2.5%. Extrapolation of the results to all type 1 diabetes patients with ESRD in Finland showed that about 1.5% of the patients incur more than 10% of all outpatient prescription medication costs. The cost of diabetes medication remains rather stable irrespective of the prevalence of complications or duration of diabetes. These costs were even lower in patients with ESRD or with both conditions than in those without complications. This observation is in accordance with patients with decreased GFR requiring a reduced amount of insulin (357). Thus, the increase of the costs in patients with these severe complications was entirely due to the costs of medication related to co-morbidity. This is not a surprise since renal failure is likely to display several co-morbidities including cardiovascular disease, secondary hyperparathyroidism, electrolyte disturbances and anaemia, as well as bone and mineral metabolism disorders, necessitating multiple pharmacological therapies.

Type 1 diabetes itself may generate 8 to 12 times higher medication costs than in non-diabetic controls (16, 17). However, there is also a large variation in costs among the patients with type 1 diabetes at different severity stages of DN, already before the development of ESRD. Overall, Study II shows that the costs of prescription medications have increased in normo-, micro- and macroalbuminuric patients over time. This trend corresponds to the general development of medication costs in Finland. The cost difference between normo- and microalbuminuric patients was, however, rather small, and the gap narrowed towards the end of follow-up. One potential explanation could lie in the early utilization of pharmacological treatments in patients at risk of renal disease, perhaps also in patients with upper normal AER or with other risk factors, including elevated BP and lipid abnormalities. Moreover, some patients may follow a non-albuminuric pathway

to renal impairment (97). In the FinnDiane Study population, about 5% of patients had impaired renal function ($\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$) with normal AER at baseline. Finally, there is also increasing evidence of spontaneous remission of albuminuria in patients with type 1 diabetes (121), probably as a consequence of pharmacological treatment, i.e. aggressive treatment of glycaemia, elevated BP and dyslipidaemia. Especially the use of agents acting on the RAAS has proven to be effective in slowing down the progression of renal disease (194-197).

In contrast, the cost difference between the micro- and macroalbuminuria groups was large, and this gap expanded towards the end of follow-up. Obviously, even before the development of ESRD, progression to more severe stages of DN increases the prevalence of multiple co-morbidities and, certainly, the consumption of medications. During the follow-up period several new and more efficient drugs, such as insulin analogues, ARBs, statins, phosphate binders, paricalcitol, calcimimetics and EPO, entered the market. As mentioned in the literature review, these new drugs are more expensive than the older ones, at least as long as they are protected by their patents.

In general, the findings observed in Studies I and II are consistent with those of previous studies, showing increases in the direct costs of diabetes at the stage of renal failure (9, 88), but also at the various stages of DN before the development of ESRD (344). However, direct comparisons of the findings are difficult due to different study designs, study populations, time periods, cost components and classifications of kidney disease. Also the accuracy of data sources varies between the studies. Despite a wide range of studies on medication costs in patients with diabetes, very few of these have considered medication costs according to the different severity stages of DN in patients with type 1 diabetes.

7.4 Which drugs are the major cost drivers (I–III)?

In patients without severe complications, the major contributor to the medication costs during the 11-year follow-up was diabetes medication (nearly 70% of total costs), followed by the cardiovascular medications (~10%) and other drugs (~20%). Although the proportion of diabetes medications was still the highest in patients with MVD only, nearly one-third of the costs were caused by cardiovascular medications and about one-quarter by other drugs. However, in the presence of ESRD or both complications, the major cost drivers were immunosuppressants, peritoneal dialytics and EPO, together accounting for 76% of the total costs in those with ESRD only and for 70% in those with both MVD and ESRD. As might be expected, the major cost drivers in the patients with kidney transplants were immunosuppressive drugs, while the proportion of diabetes medication or other drugs of the total costs was rather small. However, patients who were transplanted after the millennium had higher costs of immunosuppressive drugs than the earlier cohort. The newer immunosuppressants, MMF and tacrolimus, are more expensive than the older ones, and for obvious reasons were more common in the later cohort. Previous cost-effectiveness studies have shown that these new drugs reduce the risk of acute rejection and offer at least short-term economic advantages (358).

Shares of various medications of the total costs have also changed over time. Diabetes medications are the major cost driver, but their proportion of the total costs has decreased in all renal status groups prior to ESRD between 1995 and 2005. At the same time, the proportion of cardiovascular medications has increased in normoalbuminuric patients, while their share has been rather constant in the micro- and macroalbuminuria groups. However, the shares of medications other than diabetes or cardiovascular drugs have increased in all groups, especially in the macroalbuminuria group. Notably, in this group, EPO has become one of the major cost drivers. Taken together, these changes may again be explained by the increased use of newer medications such as statins or EPO. Also implementation of new evidence-based guidelines to tackle diabetes and its complications may be a contributing factor.

7.5 Effects of legislative measures on medication use and costs (II)

Several legislative measures, such as a reduction in VAT, wholesale price cuts and generic substitution, implemented in Finland over the past decades have only temporarily restrained the increasing trend in medication expenditures (277, 288). The most likely reason for the ascending trend is that the new patented drugs seem to have a substantial effect on the total costs of drugs. During the follow-up we observed a similar increasing trend, with a light temporal decrease in medication costs in patients with type 1 diabetes prior to ESRD. Thus, the overall increasing trend in costs reflects the general development of drug costs in Finland.

Generic substitution was introduced in Finland in 2003. While generic drugs are less expensive than branded products, they may also foster competition between pharmaceutical companies. As mentioned earlier, during the first year of generic substitution, over half of the savings came from lipid-lowering drugs and antidepressants, and one-tenth from agents acting on the RAAS (286). Interestingly, during the first year of generic substitution the consumption of cardiovascular drugs increased by 10%, but their sales value increased only by 1% (288). Correspondingly, Study II showed that in all renal status groups prior to ESRD the costs of lipid-lowering drugs and agents acting on the RAAS decreased towards the end of follow-up and prior to the introduction of generic substitution. Similarly, the consumption of these drugs simultaneously increased. This suggests that generic substitution has generated savings, but has not succeeded in curbing the ascending trend of the total costs. The reference price system was adopted and generic substitution was extended to cover drugs holding an analogue process patent in 2009. Therefore, further research needs to be focused on more recent trends in medication utilization and costs, also considering whether the reference price system has had any effect on medication costs in patients with diabetes.

7.6 Have patients been treated in accordance with ADA guidelines (IV, V)?

The ADA treatment guidelines emphasize the importance of controlling of HbA_{1C}, BP and LDL-C in patients with diabetes. Findings presented in this thesis confirm that a large gap exists between evidence-based diabetes guidelines and clinical practice since only a minority of patients with type 1 diabetes have reached the targets proposed by the ADA for these three key components. It is important to note that one-third of the patients without and two-thirds of the patients with DN had not attained any of the targets. Moreover, it seems to be surprisingly rare for an individual to meet all three targets, regardless of stage of renal disease. Results from Study V show, however, that DN is a strong predictor of failure to reach a single treatment target.

Despite advances in insulin preparations, delivery and glucose monitoring systems, glycaemic control has not improved markedly in patients with type 1 diabetes in Finland (307). Findings in Study V clearly indicate that glycaemic control is far from optimal since the median HbA_{1C} values remained above 8%, and only one-tenth of all patients reached the cut-off value of < 7%. These findings are consistent with recent reports showing that about 13% of patients with type 1 diabetes had reached the target HbA_{1C} (10, 308). In light of the DCCT/EDIC data, improvements are especially needed in those without complications and with shorter duration of diabetes, as intensive glycaemic control implemented soon after the diagnosis of diabetes is associated with long-term reduction in both micro- and macrovascular complications (i.e. “metabolic memory”) (126).

To achieve optimal glycaemic control, self-management skills, such as home blood glucose monitoring and flexible insulin dose adjustment for diet and physical activity, are essential for successfully and safely managing diabetes. Notably, the prevalence of obesity has risen in patients with type 1 diabetes (176), which can become a barrier to optimal glycaemic control. Therefore, in strategies to improve glycaemic control, more attention should also be paid to lifestyle modification, such as weight loss, exercise, dietary changes and a reduction in alcohol use, as well as assessment of mood disturbances since these factors impose barriers to the management of diabetes (177). Previous studies have shown that diabetes self-management education and support improves glycaemic control and quality of life (359-361). Also from the economic point of view, these education programmes have proven cost-effective (362). Given the fact that successful management of diabetes is challenging and complex for patients and their families, and the major responsibility for day-to-day care rests with the patients themselves, greater emphasis should be focused on improving self-management skills, reducing diabetes-related distress and improving communication between the patient and health care providers. The importance of a permanent and long-lasting patient-doctor-nurse relationship must also be stressed.

Despite current knowledge about the importance of management of hypertension and the availability of effective antihypertensive drugs, a large proportion of the patients have suboptimal BP control, which tends to worsen with progression of DN, irrespective of the number of antihypertensive drugs used. In line with the ADA recommendations, antihypertensive treatment was prescribed for most patients with micro- or

macroalbuminuria or ESRD. Moreover, nearly all antihypertensive drug-treated patients with normo-, micro- or macroalbuminuria had an ACE inhibitor or an ARB in their regimen. Even though we can not determine from Study IV (cross-sectional) whether poor BP control is a cause or consequence of DN, previous studies have shown an association between hypertension and DN and have also demonstrated that lowering of BP, especially with the use of ACE inhibitors and ARBs, may prevent the progression of DN (195-197). Thus, our findings together with the earlier studies support greater efforts being directed to those with early signs of kidney disease in order to prevent the progression to more severe stages of DN.

This suboptimal control may partly be explained by poor adherence to antihypertensive therapy, by suboptimal dosing or by inadequate use of combination therapy. About 60% of the patients with normo- and microalbuminuria who had not achieved the BP target were taking only one antihypertensive drug. However, more than half of the dialysis and 40% of macroalbuminuric and transplanted patients did not reach the target despite the concurrent use of ≥ 3 antihypertensive drugs. This suggests that the response to antihypertensive treatment may be attenuated by worsening renal function. The results are consistent with previous findings showing that advanced renal disease (both reduced eGFR and increased albuminuria) is a risk factor for therapy-resistant hypertension (310, 363-365). Moreover, our findings show that BP represents an important marker of increased risk of CVD events among DN patients. Therefore, our data suggest that it is important to identify patients with high CVD risk early in the course of diabetes and to treat their BP with a more efficient pharmacological therapy; but at the same time careful attention should be paid to improving adherence to treatment and lifestyle factors. Although the study showed that BP seems to be more difficult to control with progression of renal disease, BP is also poorly controlled among those without or with early signs of diabetic complications.

In comparison with the non-diabetic population, type 1 diabetes is associated with a higher prevalence of essential hypertension, even in the absence of DN (366, 367). The present study shows, however, slightly worse achievements for BP than in the previous studies with type 1 diabetes patients (367, 368). A possible explanation for these results may be the fact that we used office-based BP recordings from a single occasion, measured at the first FinnDiane Study visit (which might be more “exciting” than a regular visit), and these BP readings do not necessarily reflect the blood pressure variation in the patient’s usual environment. Thus, the results may overestimate the true prevalence of hypertension since we were unable to rule out a potential white coat effect. On the other hand, we did not assess the prevalence of masked hypertension, either. It may occur in 10% of patients with type 1 diabetes, and the prevalence could be even higher in patients with albuminuria (369).

Regarding LDL-C achievements at the baseline visit, only 35% of patients without DN and one-fifth of patients with DN reached the cut-off value of LDL-C. In those without DN, the median LDL-C was 2.9 mmol/L and only 7% of them were treated with lipid-lowering drugs. The corresponding numbers in those with DN were 3.3 mmol/L and 27%. Findings from the clinical trials have shown clear risk reduction of major vascular events in patients treated with statin therapy (212). Based on the current ADA guidelines, statin therapy was recommended for those with a history of CVD and for those without CVD

who are aged over 40 years and have one or more other risk factors. In the present study, the baseline data were collected between 1995 and 2004. Statins have since reached the market. In Study II, we showed an increase in the proportion of patients purchasing lipid-lowering medications during that time. It is, therefore, obvious that after the baseline visit, the proportion of patients with statin therapy has increased, which probably has had a beneficial effect on LDL-C levels.

7.7 How does resistant hypertension reflect the progression of DN (IV)?

One of the novel findings in this thesis is the high prevalence of RH in patients with type 1 diabetes. RH increased alongside the worsening of DN: while less than one-tenth of the antihypertensive drug-treated normo- or microalbuminuric patients met the criteria for RH, up to one-third of patients with macroalbuminuria and 40 % of patients on dialysis were classified as having RH. Notably, the rate was the highest in patients at the predialysis phase (eGFR 15–29). While previous studies have assessed the prevalence of RH in the general hypertensive population or the majority of the patients recruited to these studies have had type 2 diabetes, we estimated the prevalence of RH in a large and representative cohort of patients with type 1 diabetes in general and by stratifying patients according to the stage of DN. These figures are higher in antihypertensive drug-treated patients with type 1 diabetes than in the general hypertensive population: about 21% in patients with type 1 diabetes vs. 13% in patients treated for hypertension. Contrary to previous studies, we did not classify patients who had BP on target but were taking four or more antihypertensive drugs, as resistant to treatment. Even though the definition is arbitrary with regard to the number of drugs required, it assists health care professionals to identify high-risk patients who may benefit from special diagnostic and therapeutic consideration (310).

Findings from the present study suggest that a more aggressive and individualized approach to tackle the BP problem is required in patients with type 1 diabetes (309, 370). However, the downside is that aggressive treatment may cause harmful side-effects and additional costs. The first important step is to confirm the presence of uncontrolled hypertension and RH by using the correct BP measurement technique. The ambulatory measurement may provide more accurate estimates of BP, thus enabling a more accurate distinction between true and apparent RH (371). Moreover, the identification and reversal of harmful lifestyle factors, discontinuation or minimization of interfering substances and screening for secondary causes of hypertension should be considered. In addition, an efficient pharmacological regimen should be tailored for each patient, and patients' adherence to treatment should be assessed, with interventions to improve adherence should they be necessary. Finally, when a specific secondary cause of hypertension is suspected or BP remains elevated despite continuous treatment, referral to an appropriate specialist is recommended.

7.8 What might be the consequences of failure to achieve ADA targets (V)?

Numerous studies have reported the beneficial effect of controlling risk factors, including hyperglycaemia, hypertension and dyslipidaemia, in preventing CVD and premature death in patients with diabetes. We evaluated how the implementation or lack of implementation of the target values of these three key components, in the same individual simultaneously, predicts the long-term prognosis of patients with type 1 diabetes in the normal clinical setting. We found that failure to reach all of these ADA treatment targets is associated with an increased risk of CVD and all-cause mortality. Although the risk of CVD events and mortality was considerably higher in patients with DN, the failure to reach any of the three targets doubled the risk also in those without DN. Therefore, our findings strongly support the fact that successful implementation of the treatment targets for all of these key risk factors would be worthwhile for the prevention of these severe complications.

One of the interesting findings is that in patients with DN the risk of CVD event was significantly lower if BP was on target, while we did not find any differences in the risk between those who did not achieve the BP target and those who failed to achieve all three targets. Thus, BP seems to have an overwhelming effect on the CVD risk. Despite relatively high antihypertensive drug treatment rates, we show that about one-third of the patients with DN may have therapy-resistant hypertension. Accordingly, a prospective study of hypertensive chronic kidney disease patients showed that true RH was associated with an increased risk of CVD events (372). Nevertheless, this might indicate how challenging it is to treat hypertension in patients with chronic kidney disease, especially when diabetes further complicates the treatment. As also demanded by the recent scientific statement from the American Heart Association and the ADA, more work is needed to improve the understanding of the pathogenesis of CVD, hypertension and diabetic kidney disease in patients with type 1 diabetes (373). Nevertheless, our results suggest that these patients with uncontrolled BP should be identified and their BP as well as other risk factors should be addressed.

7.9 Can we identify high-risk patients by using cut-off values of HbA_{1C}, BP and LDL-C (V)?

Clinical guidelines have become an important tool for simplifying the complexity of diabetes care, and outcomes from trials represent averages derived from selected groups of people (374). The findings from the current study indicate that the cut-off values of HbA_{1C}, BP and LDL-C from the evidence-based guidelines do identify high-risk patients and might therefore be used as a rough predictor for high-risk patients. This finding should, however, be interpreted with caution for several reasons. First, the cut-off values of these three components derived from the ADA guidelines are not necessarily relevant for all patients with diabetes at different disease levels. The benefits for achieving these treatment targets depend on a large number of patient factors such as age, life expectancy, co-morbidities and self-management skills. The ADA guidelines provide one or two trigger points for some components, depending on other related factors. For example, they

recommend a more stringent LDL-C target for patients with CVD. On the other hand, the more recent ADA guidelines emphasize a more individualized approach to the management of diabetes by taking into account the patient's individual preferences, comorbidities and other patient-specific factors when deciding on treatment goals and strategies (7). In the present study, target achievement was calculated from a single measurement obtained at baseline. Unfortunately, we do not have sufficient follow-up data concerning all of these three key components. Therefore, we were unable to take into account the impact of the treatment on CVD and death risk after baseline.

Several cardiovascular risk prediction models, including the Framingham and the UKPDS Risk Engine models, are currently available. However, these models poorly predict events in patients with type 1 diabetes (375). Therefore, there is an urgent need to develop more accurate CVD risk prediction models for patients with type 1 diabetes in order to identify these high-risk patients in clinical practice. One of the promising attempts to develop such a model for this patient group was recently published by Soedamah-Muthu et al. (376). They developed a prognostic model to identify high-risk patients early in the disease process. The major outcomes included were CHD, stroke, ESRD, amputations, blindness and death. The data were analysed from participants in the EURODIAB Prospective Complications Study, and the model was also validated in three different prospective cohorts, including the FinnDiane study cohort. In that model, prognostic factors were age, HbA_{1c}, WHR, ACR and HDL-C. However, other prognostic factors, such as BP, LDL-C or smoking, were not included because of a weak additional effect. Most of the participants were recruited more than two decades ago, and it is possible that the frequency of the outcomes is different nowadays. Therefore, further efforts to test such models are needed.

The cut-off value for systolic BP has been under constant debate for years. Recently, the ADA revised the BP target from < 130/80 mmHg to < 140/80 mmHg, and this threshold has since been adopted by many national recommendations. The primary data for this new recommendation came from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which found no significant differences in the rate of major cardiovascular events or all-cause mortality when the systolic BP target was raised to < 140 mmHg (301, 302). While the previous target had been derived from observational studies, the current target was based on randomized clinical trials. Even though all patients in these trials had type 2 diabetes, this less stringent target is also recommended for patients with type 1 diabetes by the ADA. Given the fact that a subset of the patients with type 1 diabetes have a high risk of CVD and progressive kidney disease, a lower BP target (such as < 130 mmHg) may still be more appropriate, especially for younger patients (373). Relevant BP control trials focusing on type 1 diabetes to determine a specific target of BP do not exist. Randomized clinical trials focusing on the role of BP in patients with type 1 diabetes are warranted to identify appropriate BP targets and management (377).

7.10 Concluding remarks and future prospects

Pharmaceutical interventions play a fundamental role in the treatment of diabetes itself, but also in the prevention and treatment of complications. Successfully implemented

pharmacotherapy may generate savings in terms of money and intangible costs. Besides reducing the total costs of the disease, it may also improve the prognosis of patients, reduce the need for hospitalization, relieve pain and other symptoms, maintain the ability to work and function and prolong life. The costs of pharmacotherapy should always be seen as an essential part of the framework of holistic management of diabetes.

The findings presented in this thesis are observational, and therefore, we can not directly demonstrate that a lower level of proteinuria will reduce the cost of medications. Instead, we can assume that by preventing the onset or progression of DN, some patients may generate lower medication costs for some period of time. It is also clear that renal disease, especially ESRD, is the major driver of the medication costs. Despite evidence that the incidence of ESRD has decreased, the number of patients with ESRD will continue to rise worldwide due to the growing number of individuals with diabetes at increasing younger ages. This group will have enough time to develop severe complications, and a subset of them will have a high risk of micro- and macrovascular complications.

During economically uncertain times, measures bringing direct benefits and cost savings are often prioritized. The marked reductions in health care spending during the preceding economic recession in the early 1990s have weakened the care of especially patients with type 1 diabetes (378). Consequently, good clinical care has been compromised particularly in young patients with type 1 diabetes; the number of diabetes specialist nurses in diabetes care has been cut and the treatment of adults and young patients who have reached 16 years has been moved to primary health care centres. As a result, the prerequisites of good self-care have also been threatened, as treatment is allocated to institutions that do not always have sufficient resources for training and where there may be a constant lack of money and experienced, dedicated staff. Moreover, the decentralization of diabetes care to both primary health care centres and specialized care units might jeopardize the continuity of care. Finland is again facing an economic crisis, which may cause further reductions in health care spending and cuts in preventive health services. To guarantee successful management of type 1 diabetes as well as rational and efficient use of health care resources, the main focus should be placed on minimizing the risk of diabetic complications. Type 1 diabetes is a complex and psychologically demanding disease in which the day-to-day care lies primarily with the patients. This highlights the importance of long-lasting support and guidance from health care professionals. Type 1 diabetes care should be centralized to units where there is sufficient staff with different expertise to enable multiprofessional cooperation and constant education.

8 SUMMARY AND CONCLUSIONS

I The presence of ESRD increases the 11-year cumulative cost of prescription medication considerably in patients with type 1 diabetes. Extrapolation of the results to all type 1 diabetes patients showed that patients with ESRD represent only 1.5% of all patients, but this group incurs more than 10% of all prescription medication costs. The cost of diabetes medication remained quite stable regardless of the prevalence of severe complications and duration of diabetes.

II Total costs of prescription medication have increased in patients with type 1 diabetes over time, reflecting the general development of drug costs in Finland. Generic substitution has generated cost savings, but has not succeeded in halting the increasing trend, as new and more expensive patented drugs have entered the market and have been prescribed for these patients. Nevertheless, progression to more severe stages of DN has a substantial impact on costs, also before the development of ESRD, which suggests that early prevention and intensive treatment of kidney disease may generate marked cost savings.

III Total costs of prescription medication have decreased during the 9-year follow-up after kidney transplantation in patients with type 1 diabetes. The trend is mainly due to the costs of immunosuppressive drugs. This finding is consistent with the recent guidelines that recommend reducing doses of immunosuppressants over time in order to minimize undesirable side-effects. The cost levels differed between the cohorts, depending on the combination of immunosuppressive drugs in use. Those who had MFF in the regimen generated higher costs.

IV The prevalence of uncontrolled and resistant hypertension increases with worsening of diabetic kidney disease in patients with type 1 diabetes. Moreover, our findings suggest that patients with normal AER and microalbuminuria might have a suboptimal antihypertensive treatment since the majority of those who failed to reach the BP target had only one antihypertensive drug in their regimen. Thus, there is a need for a more aggressive and individualized approach to improve BP control.

V This study confirmed that a large gap exists between evidence-based guidelines and clinical practice, with only a minority of patients with type 1 diabetes reaching the ADA targets of HbA_{1C}, BP and LDL-C. Moreover, failure to achieve the targets is associated with increased risk of CVD and premature death in these patients. Although the risk was higher in patients with DN, the failure to achieve any of the three targets doubled the risk also in patients without DN. This suggests that successful implementation of the treatment targets of these three components is key for optimal prevention of CVD and mortality.

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